FORM PCT-1390 (Modified) (REV 11-98) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	
5947-01-DRK	
U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR)	
09/787657	

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/US99/23519	07 October 1999	07/10/98; 30/10/98; 29/12/98

TITLE OF INVENTION
CALCIUM CHANNEL ALPHA-2/DELTA GENE

APPLICANT(S) FOR DO/EO/US
JOHNS, Margaret Ann; MOLDOVER, Brian; OFFORD, James David

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ has been transmitted by the International Bureau.
   c. ☒ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ A copy of the International Search Report (PCT/ISA/210).
8. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
9. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
10. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 13 to 20 below concern document(s) or information included:

13. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☐ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☒ Certificate of Mailing by Express Mail
20. ☒ Other items or information:

Sequence Listing, Sequence Listing Certification and diskette containing Sequence Listing

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21. The following fees are submitted:.

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :		CALCULATIONS PTO USE ONLY
☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2) paid to USPTO and International Search Report not prepared by the EPO or JPO	$970.00	
☐ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but Internation Search Report prepared by the EPO or JPO	$840.00	
☒ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO	$690.00	
☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4)	$670.00	
☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4)	$96.00	
ENTER APPROPRIATE BASIC FEE AMOUNT =		$690.00
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).		$0.00

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	34 - 20 =	14	x $18.00	$252.00
Independent claims	17 - 3 =	14	x $80.00	$1,120.00
Multiple Dependent Claims **(check if applicable)**.			☒	$270.00
TOTAL OF ABOVE CALCULATIONS =				$2,332.00
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28) **(check if applicable)**.			☐	$0.00
SUBTOTAL =				$2,332.00
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)).			+	$0.00
TOTAL NATIONAL FEE =				$2,332.00
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).**			☐	$0.00
TOTAL FEES ENCLOSED =				$2,332.00
			Amount to be: refunded	$
			charged	$

☐ A check in the amount of to cover the above fees is enclosed.

☒ Please charge my Deposit Account No. **23-0455** in the amount of **$2,332.00** to cover the above fees.
A duplicate copy of this sheet is enclosed.

☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. **23-0455** A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

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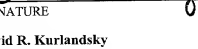

SIGNATURE

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REGISTRATION NUMBER

20 March 2001
DATE

ALPHA-2/DELTA GENE

FIELD OF THE INVENTION

The present invention relates to novel genes and polypeptides derived and identified therefrom encoding polypeptides related to the alpha-2-delta ("α2δ") protein that is a subunit of the voltage-sensitive calcium channel. In particular, three human novel genes and polypeptides derived and identified therefrom encoding three human polypeptides related to the α2δ protein are disclosed. The invention also describes vectors and host cells comprising the novel genes. The invention also describes methods for using the novel genes, polypeptides, and antibodies specifically targeting the polypeptides in the detection of genetic alterations of the gene, subcellular localization of the polypeptide, gene therapy applications, diagnostics for syndromes associated with altered α2δ expression, such as neurological diseases and disorders, diabetes, cancer, and other diseases associated with α2δ expression, and binding assays in connection with chemical databases, specifically, development of proprietary screening strategies for molecules which modify α2δ protein activity.

BACKGROUND OF THE INVENTION

The voltage activated calcium channels ("VSCCs") of vertebrates have been shown to be involved in a variety of different physiological processes including muscle contraction, insulin release from the pancreas, and neurotransmitter release in the nervous system (Greenberg D. Annals of Neurology, 1997;42:275-82; Catterall W.A., Trends in Neurosciences, 1993;16:500-506; Catterall W., Epstein P.N., Diabetologia, 35(Suppl 2:S23-33) 1992; Birnbaumer L., et al., Neuron., 1994:13; Rorsman P., et al., Diabete. Metab., 1994;20:138-145).

VSCCs are most highly expressed in excitable tissues including brain, skeletal muscle, and heart. They are multiprotein complexes composed of a

central α1 pore-forming subunit variably associated with beta, gamma, and/or an α2δ subunit. Nine different functional classes of VSCCs have been described, based on biophysical and pharmacological studies. These functional classes are mainly determined by the α1 subunit composition. The beta, gamma, and α2δ subunits modulate channel function, affecting the kinetics of activation and inactivation, voltage-dependence, peak amplitude, and ligand binding. Walker N., De Waard M., Trends in Neurosciences, 1998;21(4):148-154.

A number of compounds useful in treating various diseases in animals, including humans, are thought to exert their beneficial effects by modulating functions of voltage-dependent calcium channels. Many of these compounds bind to calcium channels and alter cellular calcium flux in response to a depolarizing signal. However, a lack of understanding of the structure of channel subunits and the genes that code for them has hampered scientists both in discerning the pharmacology of compounds that interact with calcium channels and in the ability to rationally design compounds that will interact with calcium channels to have desired therapeutic effects. The lack of understanding is due in part to the fact that it has not been possible to obtain the large amounts of highly purified channel subunits that are required to understand, at the molecular level, the nature of the subunits and their interactions with one another, with the cell membranes across which the channels allow calcium ions to pass, with calcium and other ions, and with low molecular weight compounds that affect channel function.

Further, the lack of information on genes that code for calcium channel subunits has prevented the understanding of the molecular properties of the mature calcium channel subunits and their precursor proteins (i.e., the mature subunits with signal peptides appended to the amino-terminus) and the regulation of expression of calcium channel subunits. An understanding of these properties, and of how expression of calcium channel subunits genes is regulated, may provide the basis for designing therapeutic agents which have beneficial effects through affecting calcium channel function or concentration. Furthermore, the availability of sequences of genes coding for calcium channel subunits would make possible the diagnosis of defects, which might underlie a number of diseases, in genes coding for such subunits.

Expression experiments in *Xenopus* oocytes have demonstrated that in order to produce fully functional calcium channels, the α1 and α2δ subunits must both be expressed. Absence of the α2δ subunit results in a nonfunctional channel, even though the α1 subunit, through which ions flow, is fully expressed. Indeed, not only the ion flux through these channels, but the pharmacological properties of the α1 are different in the absence of the α2δ subunit. The α2δ subunit, therefore, is a critical component of VSCCs and one that must be studied if one is to better characterize VSCC function.

A detailed understanding of VSCC operation is beginning to reveal some mechanisms for interceding in the progression of diseases associated with abnormal VSCC functions. US Patent No. 5,618,720, which issued April 8, 1997, references α1 and α2δ subunits and the polynucleotide sequences that encode the subunits. The publication, however, does not disclose any additional α2δ subunits and in light of the importance of the α2δ subunit, it can be understood that the identification and characterization of new α2δ subunits and the genes encoding these subunits would advance molecular genetic and pharmacological studies to understand the relations between the structure and the function of VSCCs.

Also, a further understanding of the biochemical mechanisms behind these subunits and their effect on mammals may lead to new opportunities for treating and diagnosing diseases related to abnormal (high or low) VSCC operation. Stated another way, a better understanding of the molecular mechanisms of VSCC operation will allow improved design of therapeutic drugs that treat diseases related to abnormal VSCC expression, and specifically abnormal α2δ expression.

The cDNAs, oligonucleotides, peptides, antibodies for the α2δ proteins, which are the subject of this invention, provide a plurality of tools for studying VSCC operations in various cells and tissues and for diagnosing and selecting inhibitors or drugs with the potential to intervene in various disorders or diseases in which altered α2δ expression is implicated. Such disease states affected include epilepsy and other seizure-related syndromes, migraine, ataxia and other vestibular defects (for review, Terwindt, GM et. Al., Eur J Hum Genet 1998 Jul-Aug; 6(4):297-307) , chronic pain (Backonja M, JAMA 1998 Dec 2;280(21):1831-6), mood, sleep interference (Rowbotham M, JAMA 1998 Dec

2;280(21):1837-42) , anxiety (Singh et al., Psychopharmocology 1996 Sep. 127(1): 1-9), ALS (Mazzini L et. Al., J Neurol Sci 1998 Oct, 160 Suppl 1:S57-63), multiple sclerosis (Metz L, Semin Neurol 1998;18(3):389-95), mania (Erfurth A, et al., J Psychiatr Res 1998 Sep-Oct;32(5):261-4), tremor (Evidente VG, et al., Mov Disord 1998 Sep;13(5):829-31), parkinsonism (Olson WL, et al., Am J Med 1997 Jan;102(1):60-6) substance abuse/addiction syndromes (Watson, WP et al., Neuropharmacology 1997 Oct;36(10):1369-75), depression, and cancer, since at least one α2δ gene is located in a region of the genome which is thought to harbor an important tumor suppressor gene (Kok K., et al., Adv Cancer Res 1997;71:27-92).

The α2δ gene is also thought to play a part in proliferative diseases other than cancer, such as inflammation. Treatment with compounds which bind to α2δ lead to changes in the signal transduction mechanism of certain proteins. This includes altered levels of MEK (eg, MEK1 and MEK2) which activates the MAP kinase. Inhibitors of MEK appear to mimic the analgesic activities associated with the binding of gabapentin to α2δ. Activation of MAP kinase by mitogens appears to be essential for proliferation, and constitutive activation of this kinase is sufficient to induce cellular transformation.

SUMMARY OF THE INVENTION

While the α1 subunit is known to be coded for by 9 genes, the beta subunit by 4 genes, and the gamma subunit by 2 genes, previously only two human α2δ genes were known: "α2δ-A (cDNA Accession No. M76559.1 and protein Accession No. P54289.1) and α2δ-B (cDNA SEQ ID NO 1 and protein SEQ ID NO 2). The α2δ-A gene codes for at least five different splice variants which show tissue-specific expression (Angelotti T., Hoffman F., FEBS, 1996;397:331-337). Translation of the α2δ-A gene produces a polypeptide which is post-translationally cleaved into the α2 and the δ subunits. A2 and δ are then joined by disulfide bonds (De Jongh K., JBC, 1990;265(25):14738-14741; Jay S., JBC, 1991;266(5):3287-3293). A2 is thought to be completely extracellular and is heavily glycosylated, while δ probably forms a single transmembrane domain with five intracellular amino acids at its c-terminus (Brickley K., FEBS,

1995;364:129-133). This transmembrane domain anchors the protein to the membrane. A2δ-B is related to α2δ-A and is available in the public database, GENBANK.

The inventors, however, have discovered the existence of two new human α2δ genes, hereinafter referred to as "α2δ-C", and "α2δ-D"genes (gene names CACNA2C and CACNA2D). The present invention, therefore, relates to the isolation of polynucleotide sequences which identify and encode novel α2δ-related proteins (preferably α2δ-C and α2δ-D proteins) that are expressed in various cells and tissues, both the polynucleotide sequences for the full length genes and any splice variants and their encoded proteins. The polynucleotide sequences are identified in SEQ ID NOS 3-4 and the amino acid sequences of the α2δ proteins encoded by the three novel genes are set forth in SEQ ID NOS 5-6.

The invention also concerns a purified or isolated nucleic acid comprising at least 20 consecutive nucleotides of the nucleotide sequences SEQ ID NOS 3-4, or a nucleotide sequence complementary thereto.

A2δ-C protein of SEQ ID NO 5 is 28% identical and 48% similar at the protein level to α2δ-A protein. A2δ-C protein is 28% identical and 47% similar to α2δ-B. A2δ-C gene of SEQ ID NO 3 contains a mapped marker (known as an STS) within its nucleotide sequence which has been mapped to human chromosome 3p21.1. This region of the human genome is thought to harbor an important tumor suppressor gene, thus α2δ-C gene is a candidate tumor suppressor gene (Kersemaekers AM, et al., Br J Cancer 1998;77(2); 192-200).

A2δ-D protein of SEQ ID NO 6 is 28% identical and 47% similar at the protein level to α2δ-A protein. A2δ-D protein is 28% identical and 46% similar to α2δ-B protein. A2δ-D gene of SEQ ID 4 maps to a previously published cosmid contig on human chromosome 12p13.3.

The unique full length polynucleotides of the present invention were initally discovered by mining the genbank database for sequences with homology to α2δ, by utilizing known nucleotide sequences and various methods known in the art, including tools provided by Compugen Systems Ltd . See Sequence Analysis Primer by Michael Gribskkov, John Devereux, Oxford University Press, 1994. After identification of expressed sequenced tags (ESTs) and full-length

sequences related to α2δ-A, cloning methods were used to obtain, in hand, full-length sequences for α2δ-C and α2δ-D, see Examples 1, 2 and 3. In short, an arrayed human, kidney cDNA library obtained from Origene, was screened by PCR, using oligonucleotide primers derived from the database sequences. Clones identified from the library screen were sequenced by standard methods for verification. A summary of the sequencing information is provided in Example 3.

Analysis of the cloned sequences for α2δ-B, α2δ-C, and α2δ-D led to the identification of a conserved domain and of a number of splice variants. The conserved domain is known as a vonWillebrand factor A3 domain (Huizinga, EG, et. al., Structure 1997, Sept 15;5(9):1147-56). This domain has been described in a large number of proteins and is thought to mediate cell adhesion. Interesting splice-variants of α2δ-C and α2δ-D were also identified. These variants result in a c-terminal truncation of the respective protein sequences. Truncation of the c-terminus may lead to the production of a soluble, secreted α2δ-C or α2δ-D protein with new functions beyond that previously described for α2δ.

The α2δ proteins are of interest because they play an important role in many disease states. In one example, α2δ-A has been shown to be a high-affinity binding target of the anti-convulsant drug gabapentin (NEURONTIN) (Gee N., JBC 1996;271:5768-5776). This property of the α2δ-A protein has the potential to have profound physiological effects. Thus, by regulating the levels or activities of α2δ-C and/or α2δ-D protein, or by modulating their function, desirable physiological effects may be obtained. Such effects may be used to treat a variety of diseases involving abnormal expression of α2δ or the abnormal expression of VSCCs (i.e., disease states include, but are not limited to epilepsy, chronic pain, anxiety, diabetes, ALS, mania, cancer, tremor, parkinsonism, migraine, ataxia, mood, sleep interference, depression, multiple sclerosis, inflammation).

The rationale for the therapeutic use of α2δ-C and/or α2δ-D proteins to design or discover treatment for these diseases is based upon the fact that gabapentin has been successfully used for treating epilepsy, chronic pain, and ALS, and has implications for use in the treatment of mania, tremor, parkinsonism, migraine, ataxia, mood, inflammation, sleep interference, and/or multiple sclerosis). Gabapentin is known to bind to α2δ-A with high affinity and

this binding is thought to represent the mechanism of action of gabapentin. Therefore, gabapentin and/or other compounds which bind to α2δ-C and/or α2δ-D proteins may have similar, or related, therapeutic effects to the effects seen with gabapentin. Also, compounds which are known to have therapeutic effects on calcium channels are regulated in their affinity by the presence of α2δ. Thus, pharmacological or genetic approaches to alleviating this deficiency will have a major impact on the diseases described above.

One aspect of the invention is to provide purified α2δ-C and/or α2δ-D proteins. The purified proteins may be obtained from either recombinant cells or naturally occurring cells. The purified α2δ-C and/or α2δ-D proteins of the invention may be mammalian in origin. Primate, including human-derived α2δ-C and/or α2δ-D proteins, are examples of the various proteins specifically provided for. The invention also provides allelic variants and biologically active derivatives of naturally occurring α2δ-C and/or α2δ-D proteins.

Another aspect of the invention is to provide polynucleotides encoding the α2δ-C and/or α2δ-D proteins of the invention and to provide polynucleotides complementary to polynucleotide coding strand. The polynucleotides of the invention may be used to provide for the recombinant expression of α2δ-C and/or α2δ-D proteins. The polynucleotides of the invention may also be used for genetic therapy purposes so as to 1) treat diseases which may result from alterations of α2δ-C and/or α2δ-D genes or from alterations of cellular pathways involving α2δ-C and/or α2δ-D, 2) test for presence of a disease, or susceptibility to a disease, due to alterations or deletions in α2δ-C and/or α2δ-D, 3) analyze or alter the subcellular localization of the α2δ-C and/or α2δ-D polypeptide, 4) clone or isolate discrete classes of RNA similar to α2δ-C and/or α2δ-D genes, 5) express discrete classes of RNA in order to alter the levels of α2δ-C and/or α2δ-D genes.

The invention also relates to oligonucleotide molecules useful as probes or primers, wherein said oligonucleotide molecules hybridize specifically with any nucleotide sequence comprising or related to the α2δ-C and/or α2δ-D genes, particularly the sequences of SEQ ID NOS 3-4. These oligonucleotides are useful

either as primers for use in various processes such as DNA amplification and microsequencing or as probes for DNA recognition in hybridization analyses.

A nucleic acid probe or primer according to the invention comprises at least 8 consecutive nucleotides of a polynucleotide of SEQ ID NOS 3-4, preferably from 8 to 200 consecutive nucleotides, more particularly from 10, 15, 20 or 30 to 100 consecutive nucleotides, more preferably from 10 to 90 nucleotides, and most preferably from 20 to 80 consecutive nucleotides of a polynucleotide of SEQ ID NOS 3 or 4. Preferred probes or primers of the invention comprise the oligonucleotides selected from the group consisting of the oligonucleotides set forth in the examples below.

The invention also concerns a method for the amplification of a region of the α2δ-C and/or α2δ-D genes. The method comprises the step of: contacting a test sample suspected of containing the desired α2δ-C and/or α2δ-D sequence or portion thereof with amplification reaction reagents, comprising a pair of amplification primers such as those described above, the primers being located on either side of the α2δ-C and/or α2δ-D nucleotide region to be amplified. The method may further comprise the step of detecting the amplification product. For example, the amplification product may be detected using a detection probe that can hybridize with an internal region of the amplified sequences. Alternatively, the amplification product may be detected with any of the primers used for the amplification reaction themselves, optionally in a labeled form.

The invention also concerns diagnostic kits for detecting the presence of at least one copy of a α2δ-C and/or α2δ-D DNA in a test sample, said kits containing a primer, a pair of primers or a probe according to the invention.

In a first embodiment, the kit comprises primers such as those described above, preferably forward and reverse primers which are used to amplify the α2δ-C and/or α2δ-D gene or a fragment thereof.

In a second embodiment, the kit comprises a hybridization DNA probe, that is or eventually becomes immobilized on a solid support, which is capable of hybridizing with the α2δ-C and/or α2δ-D gene or a fragment thereof. The

techniques for immobilizing a nucleotide primer or probe on a solid support are well-known to the skilled person.

The kits of the present invention can also comprise optional elements including appropriate amplification reagents such as DNA polymerases when the kit comprises primers, reagents useful in hybridization reactions and reagents useful to reveal the presence of a hybridization reaction between a labeled hybridization probe and the α2δ-C and/or α2δ-D gene.

Another aspect of the invention is to provide antibodies capable of binding to α2δ-C and/or α2δ-D proteins of the invention. The antibodies may be polyclonal or monoclonal. The invention also provides methods of using the subject antibodies to detect and measure expression of α2δ-C and/or α2δ-D proteins either *in vitro* or *in vivo*, or for detecting proteins that interact with α2δ-C and/or α2δ-D proteins, or molecules that regulate any of the activities of α2δ-C and/or α2δ-D proteins.

Another aspect of the invention is to provide assays for the detection of proteins that interact with α2δ-C or α2δ-D using genetic approaches. A preferred embodiment involves the use of yeast two-hybrid approaches for this screening. (Bartel and Fields, The Yeast Two-Hybrid System, Oxford University Press, 1997)

Another aspect of the invention is to provide assays for the detection or screening of therapeutic compounds that interfere with, or mimic in any way, the interaction between α2δ-C and/or α2δ-D proteins and ligands that bind to α2δ-C and/or α2δ-D proteins.

In a first embodiment, such a method for the screening of a candidate substance comprises the following steps :

a) providing a polypeptide comprising the amino acid sequence of SEQ ID NO 5 and/or 6, or a peptide fragment or a variant thereof;

b) obtaining a candidate substance;

c) bringing into contact said polypeptide with said candidate substance; and

d) detecting the complexes formed between said polypeptide and said candidate substance.

In one embodiment of the screening method defined above, the complexes formed between the polypeptide and the candidate substance are further incubated in the presence of a polyclonal or a monoclonal antibody that specifically binds to the α2δ-C and/or α2δ-D protein of the invention or to the peptide fragment or variant thereof.

The candidate substance or molecule to be assayed for interacting with the α2δ-C and/or α2δ-D polypeptide may be of diverse nature, including, without being limited to, natural or synthetic organic compounds or molecules of biological origin such as polypeptides.

In another embodiment of the present screening method, increasing concentrations of a substance competing for binding to the α2δ-C and/or α2δ-D protein with the considered candidate substance is added, simultaneously or prior to the addition of the candidate substance or molecule, when performing step c) of said method. By this technique, the detection and optionally the quantification of the complexes formed between the α2δ-C and/or α2δ-D protein or the peptide fragment or variant thereof and the candidate substance or molecule to be screened allows the one skilled in the art to determine the affinity value of said substance or molecule for said α2δ-C and/or α2δ-D protein or the peptide fragment or variant thereof.

The invention also pertains to kits useful for performing the hereinbefore described screening method. Preferably, such kits comprise a α2δ-C and/or α2δ-D protein having the amino acid sequence of SEQ ID NO 5 and/or 6 or a peptide fragment or a variant thereof, and optionally means useful to detect the complex formed between the α2δ-C and/or α2δ-D protein or its peptide fragment or variant and the candidate substance. In a preferred embodiment the detection means consist in monoclonal or polyclonal antibodies directed against the α2δ-C and/or α2δ-D protein or a peptide fragment or a variant thereof.

The assays of the invention therefore comprise the step of measuring the effect of a compound of interest on binding between α2δ-C and/or α2δ-D protein and the ligands that bind to α2δ-C and/or α2δ-D proteins. Binding may be measured in a variety of ways, including the use of labeled α2δ-C and/or α2δ-D protein or labeled ligands. These ligands may include, but are not limited to,

neutral alpha-amino acids, which have been shown to bind to α2δ-A, or therapeutic compounds such as gabapentin or related analogues.

Another aspect of the invention is to provide assays for the discovery of proteins that interact directly or indirectly with α2δ-C and/or α2δ-D proteins. The assays of the invention comprise a method for detecting such interactions in cells, or in biochemical assays. These interactions may be detected in a variety of ways, including the use of the cDNA encoding α2δ-C and/or α2δ-D proteins, or α2δ-C and/or α2δ-D proteins themselves, or fragments or modifications thereof. The assays may also comprise a method for detecting the interaction between α2δ subunits and other subunits of the calcium channel, such as α1 subunits. These assays may involve measuring the interaction between the proteins directly, or assaying the activity of a fully assembled calcium channel.

Before the present sequences, polypeptides, methods for making and using the invention are described, it is to be understood that the invention is not to be limited only to the particular sequences, polypeptides and methods described. The sequences, polypeptides and methodologies may vary, and the terminology used herein is for the purpose of describing particular embodiments. The foregoing is not intended and should not be construed as limiting the invention in any way since the scope of protection will ultimately depend upon the claims. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs. All U.S. patents and all publications mentioned herein are incorporated in their entirety by reference thereto.

BRIEF DESCRIPTION OF THE INVENTION

Figure 1: Fine-mapping of α2δ-B to mouse chromosome 9

Figure 2: Human α2δ-B tissue distribution

Figure 3: [3H] gabapentin binding activity by human α2δ–B in transiently transfected COS7

Figure 4: Human α2δ-C tissue distribution

DETAILED DESCRIPTION OF THE INVENTION

Within this application, unless otherwise stated, the techniques utilized may be found in any of several well-known references such as: *Molecular Cloning: A Laboratory Manual* (Sambrook, et al., 1989, Cold Spring Harbor Laboratory Press), *Gene Expression Technology* (Methods in Enzymology, Vol. 185, edited by D. Goeddel, 1991. Academic Press, San Diego, CA), "Guide to Protein Purification" in *Methods in Enzymology* (M.P Deutshcer, ed., (1990) Academic Press, Inc.); *PCR Protocols: A Guide to Methods and Applications* (Innis, et al. 1990. Academic Press, San Diego, CA), *Culture of Animal Cells: A Manual of Basic Technique, 2nd Ed.* (R.I. Freshney. 1987. Liss, Inc. New York, NY), and *Gene Transfer and Expression Protocols*, pp. 109-128, ed. E.J. Murray, The Humana Press Inc., Clifton, N.J.) *Sequence Analysis Primer* (Gribskov, et al., 1994, Oxford University Press).

In one aspect, the present invention provides novel isolated and purified polynucleotides, hereinafter referred to as alpha-2-delta-C and alpha-2-delta-D ("α2δ-C", "α2δ-D") genes, encoding α2δ-C and α2δ-D proteins, wherein the polynucleotide sequences are substantially similar to those shown in SEQ ID NOS 3-4 and the polypeptide sequences are substantially similar to those shown in SEQ ID NOS 5-6. The terms "α2δ-C" and "α2δ-D" are used broadly herein. Unless noted otherwise, the terms "α2δ-C" and "α2δ-D" include any natural mammalian-derived form of α2δ-C and α2δ-D and the like. It is preferred that the terms α2δ-C and α2δ-D include all mammals, including but not limited to primates and humans.

The polynucleotides provided for may encode complete α2δ-C and/or α2δ-D proteins or portions thereof. The polynucleotides of the invention may be produced by a variety of methods including *in vitro* chemical synthesis using well known solid phase synthesis technique, by cloning or combinations thereof. The polynucleotide of the invention may be derived from cDNA or genomic libraries. Persons of ordinary skill in the art are familiar with the degeneracy of the genetic code and may readily design polynucleotides that encode α2δ-C and/or α2δ-D proteins that have either partial or polynucleotide sequence homology to naturally

occurring polynucleotide sequences encoding α2δ-C and/or α2δ-D proteins. The polynucleotides of the invention may be single stranded or double stranded. Polynucleotide complementary to polynucleotides encoding α2δ-C and/or α2δ-D proteins are also provided.

Polynucleotides encoding an α2δ-C or α2δ-D protein can be obtained from cDNA libraries prepared from tissue believed to possess α2δ-C and/or α2δ-D protein or mRNA and to express it at a detectable level. For example, a cDNA library can be constructed by obtaining polyadenylated mRNA from a cell line known to express α2δ-C and/or α2δ-D protein, and using the mRNA as a template to synthesize double stranded cDNA.

Libraries, either cDNA or genomic, are screened with probes designed to identify the gene of interest or the protein encoded by it. For cDNA expression libraries, suitable probes include monoclonal and polyclonal antibodies that recognize and specifically bind to an α2δ-C or α2δ-D protein. For cDNA libraries, suitable probes include carefully selected oligonucleotide probes (usually of about 20-80 bases in length) that encode known or suspected portions of an α2δ-C or α2δ-D protein from the same or different species, and/or complementary or homologous cDNAs or fragments thereof that encode the same or a similar gene, and/or homologous genomic DNAs or fragments thereof. Screening the cDNA or genomic library with the selected probe may be conducted using standard procedures as described in Chapters 10-12 of Sambrook et al., Molecular Cloning: A Laboratory Manual, New York, Cold Spring Harbor Laboratory Press, 1989).

A preferred method of practicing this invention is to use carefully selected oligonucleotide sequences to screen cDNA libraries from various tissues. The oligonucleotide sequences selected as probes should be sufficient in length and sufficiently unambiguous that false positives are minimized. The actual nucleotide sequence(s) is/are usually designed based on regions of an α2δ protein that have the least codon redundance. The oligonucleotides may be degenerate at one or more positions. The use of degenerate oligonucleotides is of particular importance where a library is screened from a species in which preferential codon usage is not known.

The oligonucleotide must be labeled such that it can be detected upon hybridization to DNA in the library being screened. The preferred method of labeling is to use ATP (e.g., T32P) and polynucleotide kinase to radiolabel the 5' end of the oligonucleotide. However, other methods may be used to label the oligonucleotide, including, but not limited to, biotinylation or enzyme labeling.

cDNAs encoding α2δ proteins can also be identified and isolated by other known techniques of recombinant DNA technology, such as by direct expression cloning or by using the polymerase chain reaction (PCR) as described in U.S. Patent No. 4,683,195, in section 14 of Sambrook, et al , Molecular Cloning: A Laboratory Manual, second edition, Cold Spring Harbor Laboratory Press, New York, 1989, or in Chapter 15 of Current Protocols in Molecular Biology, Ausubel et al. eds., Green Publishing Associates and Wiley-Interscience 1991. This method requires the use of oligonucleotide probes that will hybridize to DNA encoding an α2δ-C and/or α2δ-D protein.

As defined herein, "substantially similar" includes identical sequences, as well as deletions, substitutions or additions to a DNA, RNA or protein sequence that maintain any biologically active portion thereof of the protein product and possess any of the conserved motifs. This includes, but is not limited to, any splice variants of α2δ-C and/or α2δ-D which are found to exist. Preferably, the DNA sequences according to the invention consist essentially of the DNA sequence of SEQ ID NOS 3-4. These novel purified and isolated DNA sequences can be used to direct expression of the α2δ-C and/or α2δ-D protein and for mutational analysis of α2δ-C and/or α2δ-D protein function.

Mutated sequences according to the invention can be identified in a routine manner by those skilled in the art using the teachings provided herein, and techniques well known in the art.

In a preferred embodiment, the present invention comprises a nucleotide sequence that hybridizes to the nucleotide sequence shown in SEQ ID NOS 3-4 under high stringency hybridization conditions. As used herein, the term "high stringency hybridization conditions" refers to hybridization on a filter support at 65°C in a low salt hybridization buffer to the probe of interest at 2×10^8 cpm/μg for between about 8 hours to 24 hours, followed by washing in 1% SDS, 20 mM

phosphate buffer and 1 mM EDTA at 65°C, for between about 30 minutes to 4 hours. In a preferred embodiment, the low salt hybridization buffer comprises between, 0.5-10% SDS, and 0.05M and 0.5 M sodium phosphate. In a most preferred embodiment, the low salt hybridization buffer comprises, 7% SDS, and 0.125M sodium phosphate.

As known in the art, numerous equivalent conditions may be employed to comprise either low or high stingency conditions. Factors such as the length and nature (DNA, RNA, base composition) of the sequence, nature of the target (DNA, RNA, base composition, presence in solution or immobilization, etc.), and the concentration of the salts and other components (e.g., the presence or absence of formamide, dextran sulfate and/or polyethylene glycol) are considered and the hybridization solution may be varied to generate conditions of either low or high stringency different from, but equivalent to, the above listed conditions.

The term "stringent conditions", as used herein, is the "stringency" which occurs within a range from about Tm-5°C (5°C below the melting temperature (Tm) of the probe) to about 20°C to 25°C below Tm. As will be understood by those of skill in the art, the stringency of hybridization may be altered in order to identify or detect identical or related polynucleotide sequences.

The polynucleotides of the invention have a variety of uses, some of which have been indicated or will be addressed in greater detail, *infra*. The particular uses for a given polynucleotide depend, in part, on the specific polynucleotide embodiment of interest. The polynucleotides of the invention may be used as hybridization probes to recover α2δ-C and/or α2δ-D proteins from genetic libraries. The polynucleotides of the invention may also be used as primers for the amplification of α2δ-C and/or α2δ-D protein encoding polynucleotides or a portion thereof through the polymerase chain reaction (PCR) and other similar amplification procedures. The polynucleotides of the invention may also be used as probes and amplification primers to detect mutations in α2δ-C and/or α2δ-D protein encoding genes that have been correlated with diseases, particularly diseases related to an altered function for α2δ-A protein. Including, but not limited to, those diseases stated above.

The invention also provides a variety of polynucleotide expression vectors, comprising α2δ-C and/or α2δ-D, or a sequence substantially similar to it subcloned into an extra-chromosomal vector. This aspect of the invention allows for *in vitro* expression of the α2δ-C and/or α2δ-D gene, thus permitting an analysis of α2δ-C and/or α2δ-D gene regulation and α2δ-C and/or α2δ-D protein structure and function. As used herein, the term "extra-chromosomal vector" includes, but is not limited to, plasmids, bacteriophages, cosmids, retroviruses and artificial chromosomes. In a preferred embodiment, the extra-chromosomal vector comprises an expression vector that allows for α2δ-C and/or α2δ-D protein production when the recombinant DNA molecule is inserted into a host cell. Such vectors are well known in the art and include, but are not limited to, those with the T3 or T7 polymerase promoters, the SV40 promoter, the CMV promoter, or any promoter that either can direct gene expression, or that one wishes to test for the ability to direct gene expression.

In a preferred embodiment, the subject expression vectors comprise a polynucleotide sequence encoding an α2δ-C and/or α2δ-D protein in functional combination with one or more promoter sequences so as to provide for the expression of the α2δ-C and/or α2δ-D protein (or an anti-sense copy of the sequence suitable for inhibition of expression of an endogenous gene). The vectors may comprise additional polynucleotide sequences for gene expression, regulation, or the convenient manipulation of the vector, such additional sequences include terminators, reporters, enhancers, selective markers, packaging sites, and the like. Detailed description of polynucleotide expression vectors and their use can be found in, among other places Gene Expression Technology: Methods in Enzymology Volume 185 Goeddel ed, Academic Press Inc., San Diego, CA (1991), Protein Expression in Animal Cells Roth ea., Academic Press, San Diego, CA (1994).

The polynucleotide expression vectors of the invention have a variety of uses. Such uses include the genetic engineering of host cells to express α2δ-C and/or α2δ-D proteins. In a further aspect, the present invention provides recombinant host cells that are stably transfected with a recombinant DNA molecule comprising α2δ-C and/or α2δ-D subcloned into an extra-chromosomal

vector. The host cells of the present invention may be of any type, including, but not limited to, bacterial, yeast, mammalian cells, and Xenopus oocytes. Transfection of host cells with recombinant DNA molecules is well known in the art (Sambrook et al., Molecular Cloning, A Laboratory Manual, 2nd ed., Cold Spring Harbor Press, 1989) and, as used herein, includes, but is not limited to calcium phosphate transfection, dextran sulfate transfection, electroporation, lipofection and viral infection. This aspect of the invention allows for *in vitro* and *in vivo* expression of α2δ-C and/or α2δ-D and its gene product, thus enabling high-level expression of α2δ-C and/or α2δ-D protein. In a further aspect of the invention the RNA molecules containing α2δ-C or α2δ-D can be injected into Xenopus oocytes along with other calcium channel subunit clones and calcium flux across the oocyte membrane can be measured using standard electrophysiological techniques.

In another aspect of the invention transgenic animals can be constructed by injection of the nucloetide sequence for α2δ-C or α2δ-D cloned in suitable expression vectors into germ cells.

Other uses of the polynucleotide expression vectors, discussed in greater detail, *infra*, include, their use for genetic therapy for diseases and conditions in which it may be desirable use to express α2δ-C and/or α2δ-D proteins at levels greater than naturally occurring expression levels. Alternatively, it may be desirable to use the subject vectors for anti-sense expression to reduce the naturally occurring levels of α2δ-C and/or α2δ-D protein.

A2δ-C and α2δ-D share amino acid homology to α2δ-A, thus it is very likely that they share some structural and functional characteristics with α2δ-A. A2δ-A is known to interact with other subunits of voltage-sensitive calcium channels, such as α1 and beta. When calcium channels are expressed in oocytes, a functional channel is only produced when an α2δ subunit is present. Therefore, α2δ is required for calcium channel function. In addition, α2δ-A has been shown to bind to gabapentin, a drug used to treat epilepsy, chronic pain, ALS, and potentially other neurological diseases. The mechanism of action of gabapentin is thought to be through its interaction with α2δ. Given the homology between the α2δ proteins, it is likely that α2δ-C and α2δ-D also share these functions.

The polynucleotide sequences of SEQ ID NOS 3-4 were mapped to human chromosomes using the nucleotide sequences for the cDNA from library sources (See Examples 2-3) to generate probes. The sequences were mapped to a particular chromosome or to a specific region of the chromosome using well known techniques. These include in situ hybridization to chromosomal spreads, and PCR-based mapping by amplifying DNA from standard radiation hybrid cell lines. (Verma et al (1988) Human Chromosomes: A Manual of Basic Techniques, Pergamon Press, NYC. A2δ-C of SEQ ID NO 3 maps to human chromosome 3p21.1. A2δ-D of SEQ ID NO 4 maps to a previously published cosmid contig on human chromosome 12p13.3.

In another aspect, the present invention provides a substantially purified recombinant protein comprising a polypeptide substantially similar to the α2δ-C and/or α2δ-D polypeptides shown in SEQ ID NOS 5-6. Furthermore, this aspect of the invention enables the use of α2δ protein in several *in vitro* assays described below. As used herein, the term "substantially similar" includes deletions, substitutions and additions to the sequences of SEQ ID NOS 5-6 introduced by any *in vitro* means, or any genetic alterations naturally seen *in vivo*. As used herein, the term "substantially purified" means that the protein should be free from detectable contaminating protein, but the α2δ-C and/or α2δ-D protein may be co-purified with an interacting protein, or as an oligomer. In a most preferred embodiment, the protein sequence according to the invention comprises an amino acid sequence of SEQ ID NOS 5-6. Mutated sequences according to the invention can be identified in a routine manner by those skilled in the art using the teachings provided herein and techniques well known in the art. This aspect of the invention provides a novel purified protein that can be used for *in vitro* assays, and as a component of a pharmaceutical composition.

A2δ-C and/or α2δ-D proteins may be used to discover molecules that interfere with its activities. For example, molecules that prevent the binding of α2δ-C and/or α2δ-D to ligands such as neutral alpha-amino acids (for example (L)-leucine), or to other molecules such as other subunits of the voltage-sensitive calcium channels.. Additionally, α2δ-C and/or α2δ-D proteins may be used to

find other proteins with which it directly interacts, and potentially representing additional important regulators of VSCC transport.

The α2δ-C and/or α2δ-D proteins of the present invention have a putative biological activity of modulating the cellular flux of calcium, potentially including both intracellular and extracellular calcium stores. The α2δ-C and/or α2δ-D protein of the invention may be isolated from a variety of mammalian animal species. Preferred mammalian species for isolation are primates and humans. The invention also contemplates allelic variants of α2δ-C and/or α2δ-D protein. A2δ-C and/or α2δ-D proteins may be prepared from a variety of mammalian tissues. Preferably, α2δ-C and/or α2δ-D proteins are obtained from recombinant host cells genetically engineered to express significant quantities of α2δ-C and/or α2δ-D proteins. A2δ-C and/or α2δ-D proteins may be isolated from non-recombinant or recombinant cells in a variety of ways well known to a person of ordinary skill in the art.

The terms "α2δ-C protein" and "α2δ-D protein" as used herein refers not only to proteins having the amino acid residue sequence of naturally occurring α2δ-C and/or α2δ-D proteins, but also refers to functional derivatives and variants of naturally occurring α2δ-C and/or α2δ-D protein. A "functional derivative" of a native polypeptide is a compound having a qualitative biological activity in common with the native α2δ-C and/or α2δ-D protein. Thus, a functional derivative of a native α2δ-C and/or α2δ-D protein is a compound that has a qualitative biological activity in common with a native α2δ-C and/or α2δ-D protein, e.g., binding to other calcium channel subunits and modulating the flux of calcium in cells, or binding to neutral alpha-amino acids and other cognate ligands. "Functional derivatives" include, but are not limited to, fragments of native polypeptides from any animal species (including human), and derivatives of native (human and non-human) polypeptides and their fragments, provided that they have a biological activity in common with a respective native polypeptide. "Fragments" comprise regions within the sequence of a mature native polypeptide. The term "derivative" is used to define amino acid sequence and glycosylation variants, and covalent modifications of a native polypeptide, whereas the term "variant" refers to amino acid sequence and glycosylation

variants within this definition. Preferably, the functional derivatives are polypeptides which have at least about 70% amino acid sequence similarity, more preferably about 80% amino acid sequence similarity, even more preferably at least 90% amino acid sequence similarity, most preferably at least about 99% amino acid sequence similarity with the sequence of a corresponding native polypeptide. Most preferably, the functional derivatives of a native α2δ-C and/or α2δ-D protein retain or mimic the region or regions within the native polypeptide sequence that directly participate in ligand binding. The phrase "functional derivative" specifically includes peptides and small organic molecules having a qualitative biological activity in common with a native α2δ-C and/or α2δ-D protein.

"Identity" or "homology" with respect to a native polypeptide and its functional derivative is defined herein as the percentage of amino acid residues in the candidate sequence that are similar to residues of a corresponding native polypeptide, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent homology. Neither N- or C-terminal extensions nor insertions, nor alternatively-spliced variants, shall be construed as reducing identity or homology. Methods and computer programs for the alignment are well known in the art.

Amino acid sequence variants of native α2δ-C and/or α2δ-D proteins and α2δ-C and/or α2δ-D protein fragments are prepared by methods known in the art by introducing appropriate nucleotide changes into a native or variant α2δ-C and/or α2δ-D protein encoding DNA, or by *in vitro* synthesis of the desired polypeptide. There are two principal variables in the construction of amino acid sequence variants: the location of the mutation site and the nature of the mutation. With the exception of naturally-occurring alleles, which do not require the manipulation of the DNA sequence encoding the α2δ-C and/or α2δ-D protein, the amino acid sequence variants of α2δ-C and/or α2δ-D protein are preferably constructed by mutating the DNA, either to arrive at an allele or an amino acid sequence variant that does not occur in nature.

Alternatively or in addition, amino acid alterations can be made at sites that differ in α2δ-C and/or α2δ-D proteins from various species, or in highly conserved regions, depending on the goal to be achieved.

Sites at such locations will typically be modified in series, e.g. by (1) substituting first with conservative choices and then with more radical selections depending upon the results achieved, (2) deleting the target residue or residues, or (3) inserting residues of the same or different class adjacent to the located site, or combinations of options 1-3.

One helpful technique is called "alanine scanning" Cunningham and Wells, Science 244, 1081-1085 (1989). Here, a residue or group of target resides is identified and substituted by alanine or polyalanine. Those domains demonstrating functional sensitivity to the alanine substitutions are then refined by introducing further or other substituents at or for the sites of alanine substitution.

After identifying the desired mutation(s), the gene encoding an α2δ-C and/or α2δ-D protein variant can, for example, be obtained by chemical synthesis.

More preferably, DNA encoding an α2δ-C and/or α2δ-D protein amino acid sequence variant is prepared by site-directed mutagenesis of DNA that encodes an earlier prepared variant or a nonvariant version of the α2δ-C and/or α2δ-D protein. Site-directed (site-specific) mutagenesis allows the production of α2δ-C and/or α2δ-D protein variants through the use of specific oligonucleotide sequences that encode the DNA sequence of the desired mutation, as well as a sufficient number of adjacent nucleotides, to provide a primer sequence of sufficient size and sequence complexity to form a stable duplex on both sides of the deletion junction being traversed. Typically, a primer of about 20 to 25 nucleotides in length is preferred, with about 5 to 10 residues on both sides of the junction of the sequence being altered. In general, the techniques of site-specific mutagenesis are well known in the art, as exemplified by publications such as, Edelman et al., DNA 2:183 (1983). As will be appreciated, the site-specific mutagenesis technique typically employs a phage vector that exists in both a single-stranded and double-stranded form. Typical vectors useful in site-directed mutagenesis include vectors such as the M13 phage. This and other phage vectors are commercially available and their use is well known to those skilled in the art.

A versatile and efficient procedure for the construction of oligodeoxyribonucleotide directed site-specific mutations in DNA fragments using M13-derived vectors was published by Zoller, M.J. and Smith, M., Nucleic Acids Res. 10, 6487-6500 [1982]). Also, plasmid vectors that contain a single-stranded phage origin of replication, Veira et al., Meth. Enzymol. 153:3 (1987)] may be employed to obtain single-stranded DNA. Alternatively, nucleotide substitutions are introduced by synthesizing the appropriate DNA fragment in vitro, and amplifying it by PCR procedures known in the art.

In general, site-specific mutagenesis may be performed by obtaining either a double-stranded or a single-stranded vector that includes within its sequence a DNA sequence that encodes the relevant protein. An oligonucleotide primer bearing the desired mutated sequence is prepared, generally synthetically, for example, by the method of Crea et al ., Proc. Natl. Acad. Sci. USA 75, 5765 (1978). This primer is then annealed with the single-stranded protein sequence-containing vector, and subjected to DNA-polymerizing enzymes such as, E. coli polymerase I Klenow fragment, to complete the synthesis of the mutation-bearing strand. Thus, a heteroduplex is formed wherein one strand encodes the original non-mutated sequence and the second strand bears the desires mutation. This heteroduplex vector is then used to transform appropriate host cells such as HB101 cells, and clones are selected that include recombinant vectors bearing the mutated sequence arrangement. Thereafter, the mutated region may be removed and placed in an appropriate expression vector for protein production.

The PCR technique may also be used in creating amino acid sequence variants of an $\alpha 2\delta$-C and/or $\alpha 2\delta$-D protein. When small amounts of template DNA are used as starting material in a PCR, primers that differ slightly in sequence from the corresponding region in a template DNA can be used to generate relatively large quantities of a specific DNA fragment that differs from the template sequence only at the positions where the primers differ from the template. For introduction of a mutation into a plasmid DNA, one of the primers is designed to overlap the position of the mutation and to contain the mutation; the sequence of the other primer must be identical to a stretch of sequence of the

opposite strand of the plasmid, but this sequence can be located anywhere along the plasmid DNA. It is preferred, however, that the sequence of the second primer is located within 500-5000 nucleotides from that of the first, such that in the end the entire amplified region of DNA bounded by the primes can be easily sequenced. PCR amplification using a primer pair like the one just described results in a population of DNA fragments that differ at the position of the mutation specified by the primer, and possibly at other positions, as template copying is somewhat error-prone.

Further details of the foregoing and similar mutagenesis techniques are found in general textbooks, such as, for example, Sambrook et al., Molecular Cloning: H Laboratorv Manual 2nd edition, Cold Spring Harbor Press, Cold Spring Harbor (1989), and Current Protocols in Molecular Biology, Ausubel et al. eds., John Wiley and Sons (1995).

Naturally-occurring amino acids are divided into groups based on common side chain properties:

(1) hydrophobic: norleucine, met, ala, val, leu, ile;
(2) neutral hydrophobic: cys, ser. tier;
(3) acidic: asp, glu;
(4) basic: asn, gin, his, lys, erg;
(5) residues that influence chain orientation: gly, pro; and
(6) aromatic: trp, tyr, pine.

Conservative substitutions involve exchanging a member within one group for another member within the same group, whereas non-conservative substitutions will entail exchanging a member of one of these classes for another. Variants obtained by non-conservative substitutions are expected to result in significant changes in the biological properties/function of the obtained variant, and may result in α2δ-C and/or α2δ-D protein variants which block α2δ-C and/or α2δ-D protein biological activities, i.e., modulation of calcium flux, or binding to neutral, alpha-amino acids. Amino acid positions that are conserved among

various species are generally substituted in a relatively conservative manner if the goal is to retain biological function.

Amino acid sequence deletions generally range from about 1 to 30 residues, more preferably about 1 to 10 residues, and typically are contiguous. Deletions may be introduced into regions not directly involved in ligand binding.

Amino acid insertions include amino- and/or carboxyl terminal fusions ranging in length from one residue to polypeptides containing a hundred or more residues, as well as intrasequence insertions of single or multiple amino acid residues. Intrasequence insertions (i.e. insertions within the α2δ-C and/or α2δ-D protein amino acid sequence) may range generally from about 1 to 10 residues, more preferably 1 to 5 residues, more preferably 1 to 3 residues. Examples of terminal insertions include the α2δ-C and/or α2δ-D proteins with an N-terminal methionyl residue, a naturally-occuring N-terminal signal sequence, an artifact of direct expression in bacterial recombinant cell culture, and fusion of a heterologous N-terminal signal sequence to the N-terminus of the α2δ-C and/or α2δ-D protein to facilitate the secretion of the mature α2δ-C and/or α2δ-D protein from recombinant host cells. Such signal sequences will generally be obtained from, and thus homologous to, the intended host cell species. Suitable sequences include STII or Ipp for E. coli, alpha factor for yeast, and viral signals such as herpes gD for mammalian cells. Other insertional variants of the native α2δ-C and/or α2δ-D protein molecules include the fusion of the N- or C-terminus of an α2δ-C and/or α2δ-D protein to immunogenic polypeptides, e.g. bacterial polypeptides such as betalactamase or an enzyme encoded by the E. cold trp locus, or yeast protein, and C-terminal fusions with proteins having a long half-life such as immunoglobulin regions (preferably immunoglobulin constant regions), albumin, or ferritin, as described in PCT published application WO 89/02922.

Since it is often difficult to predict in advance the characteristics of a variant α2δ-C and/or α2δ-D protein, it will be appreciated that screening will be needed to select the optimum variant. For this purpose biochemical screening assays, such as those described herein below, will be readily available.

In a further aspect, the present invention provides antibodies and methods

for detecting antibodies that selectively bind polypeptides with an amino acid sequence substantially similar to the amino acid sequence of SEQ ID NOS 5-6. As discussed in greater detail, *infra*, the antibody of the present invention can be a polyclonal or a monoclonal antibody, prepared by using all or part of the sequence of SEQ ID NOS 5-6, or modified portions thereof, to elicit an immune response in a host animal according to standard techniques (Harlow and Lane (1988), eds. Antibody: A Laboratory Manual, Cold Spring Harbor Press). In a preferred embodiment, the entire polypeptide sequence of SEQ ID NOS 5-6 is used to elicit the production of polyclonal antibodies in a host animal.

The method of detecting α2δ-C and/or α2δ-D antibodies comprises contacting cells with an antibody that recognizes α2δ-C and/or α2δ-D protein and incubating the cells in a manner that allows for detection of the α2δ-C and/or α2δ-D protein-antibody complex. Standard conditions for antibody detection of antigen can be used to accomplish this aspect of the invention (Harlow and Lane, 1988). This aspect of the invention permits the detection of α2δ-C and/or α2δ-D protein both *in vitro* and *in vivo*.

The subject invention provides methods for the treatment of a variety of diseases characterized by undesirably abnormal cellular levels of α2δ-C and/or α2δ-D. Diseases may be treated through either *in vivo* or *in vitro* genetic therapy. Protocols for genetic therapy through the use of viral vectors can be found, among other places, in Viral Vector Gene Therapy and Neuroscience Applications, Kaplit and Lowry, Academic Press, San Diego (1995). Gene therapy applications typically involve identifying target host cells or tissues in need of the therapy, designing vector constructs capable of expressing a desired gene product in the identified cells, and delivering the constructs to the cells in a manner that results in efficient transduction of the target cells. The cells or tissues targeted by gene therapy are typically those that are affected by the disease that the vector construct is designed to treat. For example, in the case of cancer, the targeted tissues are malignant tumors.

The genetic therapy methods of the present invention comprise the step of introducing a vector for the expression of α2δ-C and/or α2δ-D protein (or inhibitory anti-sense RNA) into a patient cell. The patient cell may be either in

the patient, i.e., *in vivo* genetic therapy, or external to the patient and subsequently reintroduced into the patient, i.e., *in vitro* genetic therapy. Diseases that may be treated by the subject genetic therapy methods include, but are not limited to epilepsy, chronic pain, ALS, mania, cancer, anxiety, diabetes, tremor, parkinsonism, migraine, ataxia, mood, sleep interference, multiple sclerosis and inflammation).

In a preferred aspect of the invention, a method is provided for protecting mammalian cells from abnormal levels of α2δ-C and/or α2δ-D in cells, comprising introducing into mammalian cells an expression vector comprising a DNA sequence substantially similar to the DNA sequence shown in SEQ ID NOS 3 or 4, that is operatively linked to a DNA sequence that promotes the expression of the DNA sequence and incubating the cells under conditions wherein the DNA sequence of SEQ ID NOS 3 or 4 will be expressed at high levels in the mammalian cells. Suitable expression vectors are as described above. In a preferred embodiment, the coding region of the human α2δ-C and/or α2δ-D gene is subcloned into an expression vector under the transcriptional control of the cytomegalovirus (CMV) promoter to allow for constitutive α2δ-C and/or α2δ-D gene expression.

In another preferred aspect of the present invention, a method is provided for treating or preventing abnormal levels of α2δ-C and/or α2δ-D in VSCCs, comprising introducing into mammalian tumor cells an expression vector comprising a DNA that is antisense to a sequence substantially similar to the DNA sequence shown in SEQ ID NOS 3 or 4 that is operatively linked to a DNA sequence that promotes the expression of the antisense DNA sequence. The cells are then grown under conditions wherein the antisense DNA sequence of SEQ ID NOS 3 or 4 will be expressed at high levels in the mammalian cells.

In a most preferred embodiment, the DNA sequence consists essentially of SEQ ID NOS 3 or 4. In a further preferred embodiment, the expression vector comprises an adenoviral vector wherein α2δ-C and/or α2δ-D cDNA is operatively linked in an antisense orientation to a cytomegalovirus (CMV) promoter to allow for constitutive expression of the α2δ-C and/or α2δ-D antisense cDNA in a host

cell. In a preferred embodiment, the α2δ-C and/or α2δ-D adenoviral expression vector is introduced into cells by injection into a mammal.

Another aspect of the invention is to provide assays useful for determining if a compound of interest can bind to α2δ-C and/or α2δ-D proteins. This binding may interfere with, or mimic, the binding of ligands to the VSCCs, or this binding may affect the function of α2δ-C and/or α2δ-D in modulating calcium flux. The assay comprises the steps of measuring the binding of a compound of interest to an α2δ-C and/or α2δ-D protein. Either the α2δ-C and/or the α2δ-D protein or the compound of interest to be assayed may be labeled with a detectable label, e.g., a radioactive or fluorescent label, so as to provide for the detection of complex formation between the compound of interest and the α2δ-C and/or α2δ-D protein. In another embodiment of the subject assays, the assays involve measuring the interference, i.e., competitive binding, of a compound of interest with the binding interaction between an α2δ-C and/or α2δ-D protein and a ligand already known to bind to α2δ-A protein. For example, the effect of increasing quantities of a compound of interest on the formation of complexes between radioactivity labeled ligand and an α2δ-C and/or α2δ-D protein may be measured by quantifying the formation of labeled ligand-α2δ-C and/or α2δ-D protein complex formation. In another embodiment of the subject assays, the assays involve measuring the alteration, i.e., non-competitive inhibition, of a compound of interest with the activity of α2δ-C and/or α2δ-D protein (compounds which bind to a different region of α2δ and inhibit α2δ activity, but don't prevent binding of ligands such as gabapentin).

Polyclonal antibodies to α2δ-C and/or α2δ-D proteins generally are raised in animals by multiple subcutaneous (se) or intraperitoneal (ip) injections of an α2δ protein and an adjuvant. It may be useful to conjugate the α2δ-C and/or α2δ-D protein or a fragment containing the target amino acid sequence to a protein that is immunogenic in the species to be immunized, e.g. keyhole limpet hemocyanin, serum albumin, bovine thyroglobulin, or soybean trypsin inhibitor using a bifunctional or derivatizing agent, for example maleimidobenzoyl sulfosuccinimide ester (conjugation through cysteine residues),

N-hydroxysuccinimide (through lysine resides), glutaraldehyde, succinic anhydride, $SOCl_2$, or R_1~N=C=NR, where R and R_1 are different alkyl groups.

Animals are immunized against the immunogenic conjugates or derivatives by combining 1 mg or 1 fig of conjugate (for rabbits or mice, respectively) with 3 volumes of Freund's complete adjuvant and injecting the solution intradermally at multiple sites. One month later the animals are boosted with 1/5 to 1/10 the original amount of conjugate in Freund's complete adjuvant by subcutaneous injection at multiple sites. Seven to 14 days later the animals are bled and the serum is assayed for anti-α2δ-C and/or α2δ-D protein antibody titer. Animals are boosted until the titer plateaus. Preferably, the animal is boosted with the conjugate of the same α2δ-C and/or α2δ-D protein, but also may be conjugated to a different protein and/or through a different cross-linking reagent. Conjugates also can be made in recombinant cell culture as protein fusions. Also, aggregating agents such as alum are used to enhance the immune response.

Monoclonal antibodies are obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally-occurring mutations that may be present in minor amounts. Thus, the modifier "monoclonal" indicates the character of the antibody as not being a mixture of discrete antibodies. For example, the anti-α2δ-C and/or α2δ-D protein monoclonal antibodies of the invention may be made using the hybridoma method first described by Kohler & Milstein, Nature 256:495 (1975), or may be made by recombinant DNA methods [Cabilly, et al, U.S. Pat. No. 4,816,567].

Antibodies can also be generated using phage display. In this approach libraries of peptides of random sequence are generated in antibody genes cloned into phage. These phage libraries are screened for antibodies by screening against the immobilized protein. (Hoogenboom-HR, Trends-Biotechnol. 1997 Feb; 15(2): 62-70)

In the hybridoma method, a mouse or other appropriate host animal, such a hamster is immunized as hereinabove described to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the protein used for immunization. Alternatively, lymphocytes may be immunized *in vitro*.

Lymphocytes then are fused with myeloma cells using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell [Coding, Monoclonal Antibodies: Principles and Practice, pp.59-103 (academic Press, 1986)].

The anti-α2δ-C and/or α2δ-D protein specific antibodies of the invention have a number of uses. The antibodies may be used to purify α2δ-C and/or α2δ-D proteins from either recombinant or non-recombinant cells. The subject antibodies may be used to detect and/or quantify the presence of α2δ-C and/or α2δ-D proteins in tissue samples, e.g., from blood, skin, and the like. Quantitation of α2δ-C and/or α2δ-D proteins may be used diagnostically for those diseases and physiological or genetic conditions that have been correlated with particular levels of α2δ-C and/or α2δ-D protein expression levels.

In a further aspect, the present invention provides a diagnostic assay for detecting cells containing α2δ-C and/or α2δ-D deletions, comprising isolating total genomic DNA from the cell and subjecting the genomic DNA to PCR amplification using primers derived from the DNA sequence of SEQ ID NOS 3 or 4.

This aspect of the invention enables the detection of α2δ-C and/or α2δ-D deletions in any type of cell, and can be used in genetic testing or as a laboratory tool. The PCR primers can be chosen in any manner that allows the amplification of an α2δ-C and/or α2δ-D gene fragment large enough to be detected by gel electrophoresis. Detection can be by any method, including, but not limited to ethidium bromide staining of agarose or polyacrylamide gels, autoradiographic detection of radio-labeled α2δ-C and/or α2δ-D gene fragments, Southern blot hybridization, and DNA sequence analysis. In a preferred embodiment, detection is accomplished by polyacrylamide gel electrophoresis, followed by DNA sequence analysis to verify the identity of the deletions. PCR conditions are routinely determined based on the length and base-content of the primers selected according to techniques well known in the art (Sambrook et al., 1989).

An additional aspect of the present invention provides a diagnostic assay for detecting cells containing α2δ-C and/or α2δ-D deletions, comprising isolating total cell RNA and subjecting the RNA to reverse transcription-PCR amplification using primers derived from the DNA sequence of SEQ ID NOS 3 or 4. This

aspect of the invention enables the detection of α2δ-C and/or α2δ-D deletions in any type of cell, and can be used in genetic testing or as a laboratory tool.

Reverse transcription is routinely accomplished via standards techniques (Ausubel et al., in Current Protocols in Molecular Biology, ed. John Wiley and Sons, Inc., 1994) and PCR is accomplished as described above.

The present invention may be better understood with reference to the accompanying examples that are intended for purposes of illustration only and should not be construed to limit the scope of the invention, as defined by the claims appended hereto.

Examples

Example 1

The sequence for human α2δ-A, c-DNA Accession No. M76559.1, was used to perform standard BLASTP searches against the Genbank non-redundant protein database and TBLASTN searches against the expressed sequence tag database (dbEST). Four full-length RNA sequences were identified (c-DNA Accession Nos. AF040709.1, AF042792.1, AF042793.1, and AB011130.1) which were highly homologous to α2δ-A. The DNA sequence of α2δ-B is provided by SEQ ID NO 1 and the amino acid sequence of α2δ-B is provided by SEQ ID NO 2. Using standard alignment tools, these four sequences were found to represent 4 different variants of the same gene. This gene was named α2δ-B. Further searches of the sequence databases, and analysis of proprietary clustered sequences generated using Compugen software, led to the identification of additional sequences related to α2δ-B. This includes human ESTs (Accession Nos. T80372.1, AA360556.1, AI563965.1, N53512.1, a mouse EST (Accession No. AA000341.1), and a sequence from C.elegans (Accession No. CAA90091.1). Since the initial identification of α2δ-B, additional related sequences have been deposited into the Genbank database. These correspond to Accession Nos. (**human**: AI027237.1, AI026646.1, AA994701.1, AA887514.1, AI275868.1, AI675521.1, AA906993.1, AA301068.1, AI884536.1, AI862563.1, AI191453.1, AI241832.1, AA534927.1, AA329137.1, AI586961.1, AA394008.1,

AW007700.1, R38827.1, AA255807.1, H11152.1, R60736.1, T16903.1, AA435601.1, AI094263.1; **mouse**: AA008996.1; **rat**: AI105056.1, AI502878.1).

A2δ-B is 53 % identical and 69% similar at the amino acid level to α2δ-A. The α2δ-B mRNA is 5482 bp long, and codes for a protein of 1145 amino acids. The three splice-variants of α2δ-B which were identified differ only in the 5' untranslated region, and do not alter the amino acid sequence. A2δ-B aligns to genomic sequence from a previously published cosmid contig on human chromosome 3p21.3. This DNA contig covers more than 600kb of sequence. The Accession Nos. for these genomic sequences are Z84493.1, Z84494.1, Z75743.1, Z75742.1, and Z84492.1. Analysis of the DNA sequences flanking α2δ-B led to the identification of genes flanking α2δ-B on human chromosome 3p21.3 which had been mapped in both human and mouse. These flanking genes include CIS, HyaL1, GNAI-2, and GNAT-1. In mouse, all of the flanking genes were localized to mouse chromosome 9, 60cM. Analysis of mapping data stored in the Mouse Genome Database, by Jackson Laboratory, led to the identification of three mouse neurological phenotypes that had been genetically mapped to the same mouse chromosome 9, 60cM region. These phenotypes include epilepsy1, ducky and tippy. Epilepsy1 and ducky both have spike-wave activity consistent with epilepsy. This tentatively maps α2δ-B to the chromosome 9, 60cM region in mouse, and identifies α2δ-B as a candidate gene for the mouse mutants ducky, tippy, and El1 (for overview of mapping data see Figure 1).

Northern and RT-PCR analysis of RNA expression levels of human α2δ-B were performed to analyze the expression pattern of α2δ-B. For Northern analysis, multiple tissue Northern blots and brain blots were obtained from Clontech. Non-isotopic DNA probes for α2δ-B were generated by PCR using SEQ ID NOS 7-8 and SEQ ID NO 1 as a template. Hybridization and washing conditions were in accordance with the manufacturer's instructions (Boehringer Mannheim). A2δ-B was found to have highest expression in lung, and was also detected in brain, heart, skeletal muscle, and at lower levels in all tissues tested (Figure 2). For the Northern blot surveying different areas of human brain, α2δ-B had the highest level of expression in the cerebral cortex, but was detected in all

areas of the human brain (Figure 2). RT-PCR expression analysis of human α2δ-B was also performed. RT-PCR analysis, using a cDNA tissue panel obtained from Clontech and SEQ ID NOS 7-8 for PCR-based gene amplication (cycles: 1X at 94 C 1', 35X at 94 C 0.5', 55 C 1', 72 C 2'; 1X at 72 C 10'), produced an expression pattern for α2δ-B consistent with results from Northern analysis. Overall, the expression pattern of α2δ-B is consistent with a proposed role of α2δ-B in epilepsy.

In order to determine if α2δ-B has functional properties comparable to α2δ-A, the ability of α2δ-B to bind to amino acids and gabapentin was measured. For this analysis, COS-7 cells were transiently transfected with the full-length porcine $\alpha_2\delta$-A, and human $\alpha_2\delta$-B genes each in the vector pcDNA3 (Invitrogen)(pcDNA3.1 for $\alpha_2\delta$-B) by the lipofectamine mediated transfection method. The cells were transfected and membranes harvested by the generic methods outlined below. The K_D for binding of [^{3}H] gabapentin to α2δ-B, as compared to α2δ-A, can be found in Table 1. Additional binding studies were performed using techniques similar to those outlined below. Alterations to the protocol are listed below under the subheading "Alternative Method for Measuring [^{3}H] Gabapentin binding". The data for these binding studies are in figure 3. Overall, the binding and Western data demonstrated that the porcine $\alpha_2\delta$-A and human $\alpha_2\delta$-B full-length gene-products expressed transiently in the COS-7 system bind [^{3}H]gabapentin with high affinity.

Table 1: Saturation binding data for α2δ-B

Porcine $\alpha_2\delta$-A (n=2)	**Human $\alpha_2\delta$-B** (n=2)
K_D, 23.1 nM	K_D, 32.6 nM
K_D, 21.2 nM	K_D, 87.2 nM
Mean = 22.2 nM	***Mean = 59.9 nM***

Transient Transfection method (150mm plate)

1: Seed 3.9 x 10^6 COS-7 cells/150mm plate in 42ml DMEM + 10% FBS + 5u/ml Penicillin / 5µg/ml Streptomycin on 150mm plate. Grow O/N.

2: Setup

Tube A – 30ug DNA in 300ul TE + 1.8ml Optimem (5u/ml Penicillin / 5µg/ml Streptomycin)

Tube B – 150ul Lipofectamine + 1.95ml Optimem (5u/ml Penicillin / 5µg/ml Streptomycin)

3: At time=0 mix tubes A and B and leave at RT for 45 minutes.

4: Wash cells with 30ml Optimem (5u/ml Penicillin / 5µg/ml Streptomycin) twice then add 16.8ml Optimem (5u/ml Penicillin / 5µg/ml Streptomycin) to the plates. At t=45 minutes add A/B mix to plates.

5: At t=6 hours add 21ml of Optimem (5u/ml Penicillin / 5µg/ml Streptomycin).

6: At t=24 hours replace medium with 42ml Optimem (5u/ml Penicillin / 5µg/ml Streptomycin)

7: At t=48 hours rinse the cells twice with 20ml of PBS then harvest.

Membrane preparation (perform at 4°C)

1 Harvest cells into a 2ml eppendorf in 1.5ml 1mM EDTA/1mM EGTA/0.1mM PMSF (added immediately prior to use from a 1000x stock)/20% Glycerol/10mM HEPES pH7.4 @ 4°C using a cell scraper.

2 Mix cells end-over-end for 30 minutes at 4°C then centrifuge at 20,000 x g for 5 minutes.

3 Resuspend pellet in 1.5ml 1mM EDTA/1mM EGTA/20% Glycerol/10mM HEPES pH7.4 @ 4°C then immediately re-centrifuge at 20,000 x g for 5 minutes.

4 Resuspend pellet to ~1mg/ml (protein concentration as determined by the Bradford protein assay) in 1mM EDTA/1mM EGTA/20% Glycerol/10mM HEPES pH7.4 @ 4°C

For total [H3] binding, cells were sonicated for 30-40 seconds, centrifuged for 10' at 750-1000Xg, and the supernatent was centrifuged for 30' at 50,000Xg. The resulting pellet was resuspended in 5mM

[^{3}H]Gabapentin saturation binding assay methodology and data analysis

Assays were carried out at 21°C in a final volume of 250µl in 96-well deep-well plates. Duplicate wells were set up for both 'total' and 'non-specific' binding. Specific binding was defined as that remaining after subtraction of the 'non-specific binding' values from the 'total' binding values. Assay components were added in the following order (all reagents were diluted in 10mM HEPES (pH 7.4 at 21°C)):

Total binding 200µl 10mM HEPES pH 7.4

Non-specific binding 175µl 10mM HEPES pH 7.4 and 25µl 100µM (S+)-3-isobutyl GABA

25µl Appropriate COS membrane sample

25µl [^{3}H]gabapentin

The reaction was incubated at 21°C for 45 minutes then filtered through GF/B filters soaked in 50 mM Tris-Cl pH 7.4 @4°C (wash buffer), filters were washed three times with wash buffer.

The filters were then counted in a scintillation counter.

Saturation experiments were performed with 12 duplicate data points ('Total' and 'Non-Specific' binding determined in duplicate for each concentration of [^{3}H]gabapentin tested) and a [^{3}H]gabapentin concentration range from ~1 to 400nM. Data was analyzed using KEL-RADLIG for Windows.

Alternative Method for Measuring [^{3}H] Gabapentin binding

The method described above was followed with the following exceptions:

1) **COS7 transfection**: 20ug of α2δ–A or α2δ–B plasmid DNA were incubated with 30ul of lipofectamine. The mixture was overlaid onto the cells in 1.5ml of serum-free medium and incubated for 5 hours. Then FBS was added to the dishes to bring the final concentration to 10%. The medium was changed the next morning. Forty-eight hours after transfection the cells were harvested for membrane preparation.

2) **Membrane preparation**: Cells were washed twice with cold PBS and then scraped off the tissue culture plates in cold 5mM of Tris/5mM EDTA (pH7.4) containing PMSF (0.1mM), leupeptin (0.02mM), and pepstatin (0.02mM). The cells were incubated on ice for 30 minutes and then sonicated for 30-40 seconds. The homogenate was centrifuged for 10 minutes at 750-1000xg, and then the supernatent was centrifuged for 30 minutes at 50,000xg. The resulting pellet was resuspended in the same buffer as described above.

3) **Binding Assays**: The radioligand binding assay was done using 0.05 mg of membrane protein incubated in the presence of 20 nM of [^{3}H] gabapentin. The membranes were incubated in 10 mM Hepes (pH 7.4) for 40-50 minutes at room temperature, and then filtered onto pre-wetted GF/C membranes and quickly washed five times with 3ml of ice cold 50mM tris buffer pH7.4. The filters were dried and counted in a liquid scintillation counter. To determine background binding, 10 uM of isobutyl GABA was used and the resulting counts subtracted from the total counts of each sample.

Detection of α2δ-A and α2δ-B expression with anti-α_2 polyclonal antibodies

Using affinity purified anti-α_2 polyclonal antibodies (antigen derived from porcine α_2δ-A; See Brown and Gee (1998) *JBC* **273** 25458-25465 for pAb

generation details) the expression of the porcine $\alpha_2\delta$-A and human $\alpha_2\delta$-B proteins (over and above control levels - COS cells transfected with the parent pcDNA3 vector) was confirmed. N.B. Cross reaction of the pAb's with $\alpha_2\delta$-B was not unexpected given the ~50% amino acid sequence identity. Furthermore, and with reference to Example 2, expression of $\alpha_2\delta$-C was not detected using this antibody (sequence identity with $\alpha_2\delta$-A ~30%).

Example 2

The sequence for human $\alpha_2\delta$-A, Accession No. M76559.1, was used to perform standard BLASTP searches against the Genbank non-redundant protein database and TBLASTN searches against the expressed sequence tag database (dbEST). EST sequences were identified (Accession Nos. AA815447.1, AA190607.1, AI223142.1, AA188635.1, R43629.1, R20288.1, AA459684.1, AA662058.1, Z44942.1, Z40693.1, AI051759.1) corresponding to a new gene, with similarity to $\alpha_2\delta$-A, named $\alpha_2\delta$-C. Additional searches of the sequence databases led to the identification of other sequences related to $\alpha_2\delta$-C. This includes a mouse EST (Accession No. AU022914.1, AI843362.1), and an STS (Accession No. G36524.1) which maps to human chromosome 3p21.1. Since the initial identification of $\alpha_2\delta$-B, additional related sequences have been deposited into the Genbank database. These correspond to Accession Nos. (human ESTs: AA459804.1, AI696320.1, AI051759.1, AI696214.1; human genomic sequence: AC010180.1; mouse EST: AA445859.1, mouse RNA: AJ010949.1).

In order to clone a full-length $\alpha_2\delta$-C, a PCR-based cDNA library screen was carried out by Origene using primers (SEQ ID NOS 9-10) based on sequence derived from EST clone accession number AA190607.1 which were designed to amplify a 273 bp fragment. A positive clone was identified in a kidney library. After sequencing, this clone was identified as a novel 3' splice variant (SEQ ID NO 43). The protein sequence, which can be derived from SEQ ID NO 43, of this novel splice variant is a truncated, potentially secreted soluble form of $\alpha 2\delta$-C. PCR was performed, using primers (SEQ ID NOS 9 and 11) and a human adult

brain library from LTI as a template, and the resulting fragment of 248 bp was cloned in pBS and sequence verified. A SacI-NcoI fragment from the kidney clone, a NcoI-KpnI fragment from the PCR center clone, and a KpnI-NotI fragment from a clone obtained from the IMAGE consortium (corresponding to Accession No. R43629.1) were ligated together, using methods standard to the art, to create a full-length clone. Each individual clone, and the full-length clone (SEQ ID NO 3), were sequence verified. A number of other EST clones from the IMAGE consortium were also obtained and sequenced. One of these clones (corresponding to Accession No. AI051759.1) contained a two novel splice-variants which result in a truncated, potentially soluble $\alpha_2\delta$-C (SEQ ID NO 44).

Full-length $\alpha_2\delta$-C is 28 % identical and 48% similar at the amino acid level to $\alpha_2\delta$-A. The $\alpha_2\delta$-C mRNA sequence (SEQ ID NO 3) is 3770 bp long, and codes for a protein of 1085 amino acids (SEQ ID NO 5). In addition, three splice variants of $\alpha_2\delta$-C were identified . Two of the variants contain deletions of internal exons. The third variant contains a novel 3' end. Two of these splice-variants produce a truncated protein which is devoid of the membrane anchoring delta subunit. These variants may represent a secreted alpha2 protein which could have additional functions beyond regulation of voltage-sensitive calcium channels.

In order to identify sequences for $\alpha_2\delta$-C from other species, human and mouse specific primers (SEQ ID NOS 9-10 and 12-13, respectively) were used to amplify $\alpha_2\delta$–C RT-PCR products. RNA from human brain was purchased from Invitrogen, Carlsbad, CA (catalog #D6030-15). RNA from rat and mouse brain was isolated using standard in-house protocols. First-strand cDNA synthesis was completed using Superscript Choice System (LTI, Bethesda, MD, catalog #18090-019). Ethanol precipitated cDNA was added to PCR mix containing 1X PCR buffer, 0.2mM dNTP, 10pmol/well forward primer, 10pmol/well reverse primer, and 0.5 units Platinum TAQ High Fidelity (LTI, Bethesda, MD). Products were amplified at 95 °C for 5 minutes, followed by 35 cycles of 95 °C for 1 minute, 58° C for 1 min, 68° C for 2 minutes, and final extension at 72 °C for 10 minutes. PCR products were assayed on 1% agarose (TAE) gels at 100 volts for 45 minutes. Gels were visualized under UV and photographed. Products

were purified using Millipore Ultrafree-MC PCR purification filter units (catolog # UFC3LTKOO) prior to DNA sequence analyses. Using this approach, three sets of primers (SEQ ID NO 36, 37; SEQ ID NO 12, 13, SEQ ID NO 38, 39) where used for PCR amplification of rat $\alpha 2\delta$-C. Three partial rat sequences for $\alpha 2\delta$-C were identified (SEQ ID NOS 40, SEQ ID NO 14, SEQ ID NO 41).

RT-PCR analysis of RNA expression levels were performed to analyze the expression pattern of $\alpha_2\delta$-C. cDNA Expression Panels were purchased from OriGene Technologies, Inc. (Rockville, Maryland). Human (catalog # HSC-101) and Mouse (catalog # MSCB-101) cDNAs from 24 tissue sources were pre-arrayed in a 96-well PCR format. PCR mix containing 1X PCR buffer, 0.2mM dNTP, 10pmol/well forward primer, 10pmol/well reverse primer, and 0.5 units Platinum TAQ (LTI, Bethesda, MD) was added to each well. Products were amplified at 95 °C for 5 minutes, followed by 35 cycles of 95 °C for 1 minute, 58° C for 1 min, 68° C for 2 minutes, and final extension at 72 °C for 10 minutes. PCR products were assayed on 1% agarose (TAE) gels at 100 volts for 45 minutes. Gels were visualized under UV and photographed. The primers used for this amplification from the human template correspond to SEQ ID NOS 9-10, and from the mouse template correspond to SEQ ID NOS 12-13. By RT-PCR, $\alpha 2\delta$-C was found to be expressed in a wide variety of tissues (Table 2). The highest levels of $\alpha_2\delta$-C were detected in human brain, and also in human testis and kidney. In addition to RT-PCR, the cDNA sequence for this gene has been detected in a human, adult brain library and also libraries from: infant brain, hNT neural cell line, testis, total fetus, alveolar rhabdomyosarcoma, adenocarcinoma, and a pooled germ cell library.

Northern blot analysis was performed using $\alpha 2\delta$-C as a probe. Human total RNA was obtained from Invitrogen (Carlsbad, CA) (brain. total RNA(Cat #D6030-01), kidney total RNA (Cat #D6070-01), testis total RNA(Cat #D6121-01), liver total RNA(Cat # D6080-015)) or Ambion Inc(Austin, TX)(placenta total RNA Cat#7950, heart total RNA Cat #7966), lung total RNA(Cat #7968)) RNA was electrophoresed in formaldehyde agarose gels then transferred to charged nylon membranes(Ambion Inc. (Austin TX) Cat #10104. The EST clone (SEQ ID NO 47) was digested with BamHI and used as template in an RNA synthesis

reaction that yielded 32P labeled probe. The nylon membranes containing the RNA were prehybridized for 2 hours in ExpressHyb hybridization solution (Clontech Inc. (Palo Alto, CA)(Cat # 8015-1). After the prehybridization 4X106 cpm of RNA probe labeled with 32P wre added to the solution and the hybridization was performed in the same solution for 2 hours. After hybridization the nylon filter was washed for 1 hour with 4 changes of 2X SSC, 0.5% SDS at room temperature. The nylon filter was transferred to a solution of 0.2X SSC, 0.5% SDS at 68°C and washed with 4 changes of solution. The nylon filters were then exposed to phosphoroimager screens Molecular Dynamics(Sunnyvale, CA)and read on a Storm phosphorimager.Molecular Dynamics(Sunnyvale, CA). Results from Northern analysis (Figure 4) indicate that $\alpha 2\delta$-C has highest levels of expression in human brain, kidney, and testis.

Since $\alpha_2\delta$-C has sequence homology to $\alpha_2\delta$-A, and $\alpha_2\delta$-A functions as a subunit of VSCCs, experiments were undertaken to determine if $\alpha_2\delta$-C can replace $\alpha_2\delta$-A and produce functional VSCCs. Xenopus oocytes were isolated using standard techniques and injected with cRNA for α_{1B}, β_{1C} and $\alpha_2\delta$-C subunits of voltage-gated Ca^{2+} channels. Four days to 1 week following injection of cRNA, Ca^{2+} channel currents were measured using two-electrode voltage clamp with 5 mM Ba^{2+} as the charge carrier. Test pulses to +10 mV from a holding membrane potential of –80 mV were applied to evoke Ca^{2+} channel currents. Peak inward currents evoked during the test pulse were measured. The amplitude of inward currents is proportional to the expression level of voltage-gated Ca^{2+} channels.

Expression of α_{1B}, β_{1C} without $\alpha_2\delta$ subunits produced currents with an average amplitude of 105 ± 13 nA (n=20). Co-injection of $\alpha_2\delta_c$ with α_{1B} and β_{1C} subunits produced a significant increase in current amplitude to 213 ± 12 nA (n=20, $p < 0.01$ compared to no $\alpha_2\delta$ subunits). These data suggest that $\alpha_2\delta_C$ has an effect on Ca^{2+} channels similar to $\alpha_2\delta_A$, enhancing the level of channel expression. However, $\alpha_2\delta_c$ did not produce as large of an effect on channel expression as $\alpha_2\delta_A$, producing a 2-fold increase in current compared to a 20-fold increase observed with the co-injection of $\alpha_2\delta_A$. Overall, these initial functional

studies indicate that $\alpha_2\delta$-C can replace $\alpha_2\delta$-A in voltage-sensitive calcium channels after co-injection into Xenopus oocytes with the $\alpha 1$ and beta subunits.

Table 2: RT-PCR EXPRESSION PROFILE FOR ALPHA2-DELTA C

Tissue	*Human a2d-C*	*Mouse a2d-C*
Brain	+++	+
Heart	++++	-
Kidney	++	++
Liver	-	-
Colon	+	not assayed
Lung	+	++
Small Intestine	++	+
Muscle	++++	++
Stomach	++	-
Testis	+++	++
Placenta	++	not assayed
Salivary Gland	++	not assayed
Thyroid Gland	++	not assayed
Adrenal Gland	++	-
Pancreas	++	not assayed
Ovary	++	-
Uterus	++	-
Prostrate	++	++
Skin	++	-
PBL	-	not assayed
Bone Marrow	-	not assayed
Fetal Brain	++	not assayed
Fetal Liver	++	not assayed

Example 3

The sequence for human $\alpha 2\delta$-A, Accession No. M76559.1, was used to perform BLASTP searches against the Genbank non-redundant protein database

and TBLASTN searches against the expressed sequence tag database (dbEST). EST sequences were identified (Accession No. T70594.1,T96901.1,AA766033.1, AI160471.1, AA719773.1, AI003601.1, AA442451.1, AA521470.1, AA770076.1, AA001411.1, AA001473.1, W22650.1, H86016.1) corresponding to a new gene, with similarity to α2δ-A, named α2δ-D. Additional searches of the sequence databases led to the identification of other sequences related to α2δ-D. This includes genomic sequence derived from human chromosome 12p13.3 (Accession No. AC005342.1, AC005343.1). Since the initial identification of α2δ-D, additional related sequences have been deposited into the Genbank database. These sequences correspond to Accession Nos. (human ESTs: T96900.1, AI457823.1, AI377638.1, and AI433691.1).

To isolate a full-length α2δ-D clone, a PCR-based cDNA library screen was carried out by Origene using primers (SEQ ID NOS 18-19) based on sequence derived from EST clone Accession No. AA001473.1 which were designed to amplify a 372 bp fragment. A positive clone was identified in a placental library, and was confirmed using a nested internal primer (SEQ ID NO 20). This clone was fully sequenced. The sequence extended 350 bp 5' of the sequence obtained from the EST sequences, but did not include the 5' end.

To obtain the 5' end, two approaches were undertaken One approach utilized 5' RACE (Rapid Amplification of cDNA Ends). For 5' RACE, placenta poly A+ RNA from Clontech was used to construct a RACE-ready cDNA library using a Marathon cDNA Amplification kit purchased from Clontech. The 5'-end sequence of α2δ-D was obtained by 5' RACE PCR using first set of primers: Marathon cDNA adapter primer 1 (SEQ ID NO 45) and gene specific primer I (SEQ ID NO 21). The PCR product was re-amplified using a set of nested primers: adapter primer 2 (SEQ ID NO 46) and gene specific primer II (SEQ ID NO 22). A resulting 1 kb PCR product was cloned into a TA vector (Invitrogen) and sequenced. Sequence analysis revealed that it contains the 5' sequence of α2δ-D.

A second method undertaken to identify the 5' end of α2δ-D was a PCR-based library screen performed by Edge, using the 5' most sequence known for α2δ-D. Nine clones were PCR amplified by the methods indicated above, for

verification using primers with SEQ ID NOS 48 and 49. These nine positive clones were then sequenced for verification by standard methods. All nine clones were identical to each other, and all were short of the 5' end by approximately 500 bp. However, these clones contained novel splice-variants of α2δ-D, with insertions of novel nucleotide sequences (SEQ ID NO 16).

The full-length sequence of α2δ-D is 28 % identical and 47% similar at the amino acid level to α2δ-A. The α2δ-D mRNA is 5,073 bp long (SEQ ID NO 4), and codes for a protein of 1120 amino acids (SEQ ID NO 6) . In addition, two splice variants of α2δ-D were identified. One of the variants contains a 72 bp deletion of an internal exon (SEQ ID NO 15). The amino acid sequence of this variant can be found in SEQ ID NO 17. The second variant contains two novel insertions, one of 338 bp and one of 305 bp (SEQ ID NO 16). These insertions appear to result in a truncated protein (SEQ ID NO 42), comparable to the truncated protein sequence identified for α2δ-C in Example 2.

RT-PCR analysis of RNA expression levels of human $\alpha_2\delta$–D were performed in order to analyze the tissue distribution of α2δ-D. cDNA Expression Panels were purchased from OriGene Technologies, Inc. (Rockville, Maryland). Human (catalog # HSC-101) and Mouse (catalog # MSCB-101) cDNAs from 24 tissue sources were pre-arrayed in a 96-well PCR format. PCR mix containing 1X PCR buffer, 0.2mM dNTP, 10pmol/well forward primer, 10pmol/well reverse primer, and 0.5 units Platinum TAQ (LTI, Bethesda, MD) was added to each well. Products were amplified at 95 °C for 5 minutes, followed by 35 cycles of 95 °C for 1 minute, 58° C for 1 min, 68° C for 2 minutes, and final extension at 72 °C for 10 minutes. PCR products were assayed on 1% agarose (TAE) gels at 100 volts for 45 minutes. Gels were visualized under UV and photographed. In the case of the α2δ-D human panels two separate sets of primers were used to distinguish splice variants and wild type species (SEQ ID NOS 18 & 20, SEQ ID NOS 23 & 19, respectively).

Analysis of the results from RT-PCR of $\alpha_2\delta$-D (see Table 3) indicate that $\alpha_2\delta$-D is expressed in a wide variety of tissues, with highest levels in placenta, adrenal gland and pancreas, but also detected in all tissues other than colon. Of note, α2δ-D was detected in human brain, consistent with a potential role in

neurological disease. In addition, based on the tissue distribution of EST sequences, the cDNA sequence for $\alpha_2\delta$-D has been detected in human libraries from: adult brain, retina, fetal liver/spleen, fetal heart, pineal gland, and testis.

Table 3. RT-PCR EXPRESSION PROFILE FOR ALPHA2-DELTA D

Tissue	Human *α2δ*–D **	Human *α2δ*–D
Brain	+++	+++
Heart	+++	-
Kidney	+++*	-
Liver	++	-
Colon	-	-
Lung	++	-
Small Intestine	+*	-
Muscle	++	-
Stomach	++	-
Testis	+++	-
Placenta	++++*	-
Salivary Gland	++	++++
Thyroid Gland	+++	++++
Adrenal Gland	++++	+++
Pancreas	++++*	++
Ovary	++*	++
Uterus	+*	++
Prostrate	++*	+
Skin	+	-

PBL	+++		-
Bone Marrow	+++		-
Fetal Brain	+++		-
Fetal Liver	++		-

*2 products: wt and splice variant
** Primers d2+dhD-2 detects splice region

Example 4. Knockout of α2δ-B

In order to create a mouse knockout of α2δ-B, Genome Systems (Catalog: BAC 4922 Mouse ES 129Svj PCR based Library Screen) performed a PCR-based screen of a mouse BAC library using primers SEQ ID NOS 25-26, which were predicted to amplify an 650 bp cDNA or genomic fragment. One positive BAC clone (Genome Systems DNA control number: BAC-22401) from this screen was received. The same primers were used to generate a human DNA probe. This probe was used on a Southern blot to identify a ~10kb HindIII mouse genomic fragment from the BAC, which was subcloned into the HindII site of plasmid vector pRS416 (Stratagene). Two separate subclones were sequenced by standard techniques, using the T3 and T7 primers and SEQ ID NOS (25-32). Two 500 bp regions of sequence from the 5' and 3' ends of the 10kb genomic fragment (SEQ ID NOS 33 and 34, respectively), plus a 1.8kb sequence contig (SEQ ID NO 35) were identified. This genomic sequence can be used to identify the intron/exon structure of a portion of mouse α2δ-B gene, and may contain regulatory elements important for α2δ-B gene expression.

Example 5. Identification of amino acids encoded by α2δ gene

The amino acid sequences of α2δ-C and α2δ-D, indicated in SEQ ID NOS 5 and 6, were determined by translating the nucleotide sequences described in SEQ ID NOS 3 and 4, and aligning the amino acid sequences of α2δ-A, α2δ-B, α2δ-C, and α2δ-D. The correct open reading frame for each amino acid sequence was determined based on homology of the amino acid sequences to other α2δ-A

homologs. At the amino acid level, α2δ-C is 28% identical and 48% similar to α2δ-A and is 28% identical and 47% similar to α2δ-B, and α2δ-D is 28% identical and 47% similar to α2δ-A and is 28% identical and 46% similar to α2δ-B. Although α2δ-C and α2δ-D are related to α2δ-A, they are distinctly new and different genes.

Example 6. Proposed method of detecting the α2δ-C and α2δ-D proteins by using an α2δ–C and α2δ-D antibody

Antibodies could be developed which specifically detect epitopes unique to α2δ-C and α2δ-D, or which detect all α2δ proteins. These antibodies could be developed by either synthesizing a peptide which is identical to α2δ-C and/or α2δ-D, or by bacterially-expressing a fusion protein containing either α2δ-C or α2δ-D, and then injecting these peptides into a research animal in order to stimulate an immunogenic response. Antibodies generated in such a manner could be used to detect levels of α2δ-C and/or α2δ-D protein in cells. This could be done by immunocytochemistry, where whole cells are fixed and then the antibody is used on the whole cells to detect expression of α2δ-C or α2δ-D, and to detect the subcellular localization of α2δ-C or α2δ-D. Or, cells may be lysed and protein extracts generated and analyzed for α2δ-C and/or α2δ-D expression.

Example 7. Isolation of RNA for cDNA Library

In order to isolate α2δ-C or α2δ-D from cells, RNA could be isolated by lysing cells from any tissue of interest using standard methods known in the field. After isolation, RNA is reverse-transcribed into cDNA using the enzyme reverse transcriptase and a poly(T) primer or a mix of random primers. A mix of cDNA is produced, representing a large number of the genes which are expressed in the beginning cell population at a particular point in time. Once the cDNA pool has been created, it can be restricted and then ligated into a cloning vector using methods standard in the field. This results in a cDNA library.

Example 8. cDNA Cloning Procedure

A2δ-C or α2δ-D could be cloned from a cDNA library, created as above, by using primers specific for α2δ-C or α2δ-D nucleotide sequences in a polymerase chain reaction, with the cDNA used as a template. Alternatively, α2δ-C or α2δ-D sequences could be used as a probe in order to screen the cDNA library by hybridization. Using either technique, single clones are ulimately isolated from the library and sequenced using standard techniques. By sequencing multiple clones from a library, one could look for the existence of alternatively-spliced variants of α2δ-C or α2δ-D, or for the existence of single nucleotide polymorphisms, or for mutations/alterations in α2δ-C or α2δ-D.

Example 9. Screening cDNA Library with Antibody

A cDNA library could also be screened by using an antibody to α2δ-C or α2δ-D. The cDNA library is cloned into a vector which allows induction of protein expression of the cloned inserts. The complete cDNA library is induced to express a protein representing the cloned insert, then single clones which contain an insert that codes for α2δ-C or α2δ-D are identified if they hybridize to an antibody generated against α2δ-C or α2δ-D. Positive clones are isolated, and then sequenced using standard methods.

It is to be understood that the invention is not to be limited to the exact details of operation, or to the exact compounds, compositions, methods, procedures or embodiments shown and described, as obvious modifications and equivalents will be apparent to one skilled in the art, and the invention is therefore to be limited only by the full scope of the appended claims.

We claim

1. An isolated and purified DNA sequence substantially similar to the DNA sequence shown in SEQ ID NOS 3 or 4.

2. An isolated and purified DNA sequence that hybridizes to the DNA sequence shown in SEQ ID NOS 3 or 4 under high stringency hybridization conditions.

3. An isolated and purified DNA sequence that consists essentially of the DNA sequence shown in SEQ ID NOS 3 or 4.

4. An isolated and purified DNA sequence that has at least a 70% identity to a polynucleotide encoding the polypeptide expressed by SEQ ID NOS 5 or 6.

5. An isolated and purified DNA sequence that is fully complementary to the DNA sequence shown in SEQ ID NOS 3 or 4.

6. A recombinant DNA molecule comprising the isolated and purified DNA sequence of Claim 3 or 4 subcloned into an extra-chromosomal vector.

7. A recombinant host cell comprising a host cell transfected with the recombinant DNA molecule of Claim 6.

8. A substantially purified recombinant polypeptide, wherein the amino acid sequence of the substantially purified recombinant polypeptide is substantially similar to the amino acid sequence shown in SEQ ID NOS 5 or 6.

9. A substantially purified recombinant polypeptide of Claim 8, wherein the polypeptide has at least about 70% amino acid sequence similarity to the amino acid sequence shown in SEQ ID NOS 5 or 6.

10. A substantially purified recombinant polypeptide, wherein the amino acid sequence of the substantially purified recombinant polypeptide consists essentially of the amino acid sequence shown in SEQ ID NOS 5 or 6.

11. An antibody that selectively binds polypeptides with an amino acid sequence substantially similar to the amino acid sequence of Claim 8.

12. A method of detecting α2δ-C or α2δ-D protein in cells, comprising contacting cells with the antibody of Claim 11 and incubating the cells in a manner that allows for detection of the α2δ-C or α2δ-D protein-antibody complex.

13. A diagnostic assay for detecting cells containing α2δ-C or α2δ-D mutations, comprising isolating total genomic DNA from the cell and subjecting the genomic DNA to PCR amplification using primers derived from the isolated and purified DNA sequence of Claim 1, 2, or 3 or by analyzing the genomic DNA directly by a hybridization method and determining whether the resulting PCR product contains a mutation.

14. A diagnostic assay for detecting cells containing α2δ-C or α2δ-D mutations, comprising isolating total cell RNA, subjecting the RNA to reverse transcription-PCR amplification using primers derived from the isolated and purified DNA sequence of Claim 1, 2, or 3 and determining whether the resulting PCR product contains a mutation.

15. A method for the amplification of a region of the DNA sequence of Claim 1, 2, or 3, the method comprising the step of: contacting a test sample suspected of containing the desired sequence of Claim 1, 2, or 3 or portion thereof with amplification reaction reagents.

16. A diagnostic kit for detecting the presence of at least one copy of the DNA sequence of Claim 1, 2, or 3 in a test sample, said kits containing a primer, a pair of primers or a probe, and optionally amplification reagents .

17. An assay for the detection or screening of therapeutic compounds that interfere with or mimic the interaction between the polypeptide of Claim 8, 9, or 10 and ligands that bind to the polypeptide of Claim 8, 9, or 10.

18. The assay of Claim 17, herein the assay comprises the steps of:

a) providing a polypeptide of Claim 8, 9, or 10;

b) obtaining a candidate substance;

c) bringing into contact said polypeptide with said candidate substance; and

d) detecting the complexes formed between said polypeptide and said candidate substance.

19. A method for protecting mammalian cells from abnormal calcium flux, comprising introducing into mammalian cells an expression vector comprising the isolated and purified DNA sequence of Claim 1, 2, or 3, which is operatively linked to a DNA sequence that promotes the high level expression of the isolated and purified DNA sequence in mammalian cells.

20. A method for treating or preventing epilepsy, comprising introducing into a mammal an expression vector comprising the isolated and purified DNA sequence of Claim 1, 2, or 3, which is operatively linked to a DNA sequence that promotes the high level expression of the antisense strand of the isolated and purified DNA sequence in mammalian cells.

21. A method for purifying α2δ-C or α2δ-D protein from cells, comprising:

a) transfecting a host cell with a vector comprising the isolated and purified DNA sequence of Claim 1, 2, or 3 operatively linked to a promoter capable of directing gene expression in a host cell;

b) inducing expression of the isolated and purified DNA sequence in the cells;

c) lysing the cells;

d) isolating α2δ-C or α2δ-D protein from the cells ; and

e) purifying α2δ-C or α2δ-D protein from the isolate.

22. An isolated and purified DNA sequence substantially similar to the DNA sequence shown in SEQ ID NOS 11, 14-16, 21-24, 31-35, 40-41, 43-44, 47-48 or 49.

23. An isolated and purified DNA sequence that hybridizes to the DNA sequence shown in SEQ ID NOS SEQ ID NOS 11, 14-16, 21-24, 31-35, 40-41, 43-44, 47-48 or 49 under high stringency hybridization conditions.

24. An isolated and purified DNA sequence that consists essentially of the DNA sequence shown in SEQ ID NOS SEQ ID NOS 11, 14-16, 21-24, 31-35, 40-41, 43-44, 47-48 or 49.

25. An isolated and purified DNA sequence that has at least a 70% identity to a polynucleotide encoding the polypeptide expressed by SEQ ID NOS SEQ ID NOS 11, 14-16, 21-24, 31-35, 40-41, 43-44, 47-48 or 49.

26. An isolated and purified DNA sequence that is fully complementary to the DNA sequence shown in SEQ ID NOS SEQ ID NOS 11, 14-16, 21-24, 31-35, 40-41, 43-44, 47-48 or 49.

27. A substantially purified recombinant polypeptide, wherein the amino acid sequence of the substantially purified recombinant polypeptide is substantially similar to the amino acid sequence shown in SEQ ID NOS 17 or 42.

28. A substantially purified recombinant polypeptide of Claim 26, wherein the

polypeptide has at least about 70% amino acid sequence similarity to the amino acid sequence shown in SEQ ID NOS 17 or 42.

29. A substantially purified recombinant polypeptide, wherein the amino acid sequence of the substantially purified recombinant polypeptide consists essentially of the amino acid sequence shown in SEQ ID NOS 17 or 42.

30. An antibody that selectively binds polypeptides with an amino acid sequence substantially similar to the amino acid sequence of Claim 26.

31. A method of using polynucleotide sequences to treat diseases which may result from alterations of α2δ-C and/or α2δ-D genes or from alterations of cellular pathways involving α2δ-C and/or α2δ-D, wherein the polynucleotide sequences are selected from the group consisting essentially of: M76559.1, AF040709.1, AF042792.1, AF042793.1, AB011130.1, T80372.1, AA360556.1, AI563965.1, N53512.1, AA000341.1, CAA90091.1, AI027237.1, AI026646.1, AA994701.1, AA887514.1, AI275868.1, AI675521.1, AA906993.1, AA301068.1, AI884536.1, AI862563.1, AI191453.1, AI241832.1, AA534927.1, AA329137.1, AI586961.1, AA394008.1, AW007700.1, R38827.1, AA255807.1, H11152.1, R60736.1, T16903.1, AA435601.1, AI094263.1, AA008996.1, AI105056.1, AI502878.1, Z84493.1, Z84494.1, Z75743.1, Z75742.1, Z84492.1, AA815447.1, AA190607.1, AI223142.1, AA188635.1, R43629.1, R20288.1, AA459684.1, AA662058.1, Z44942.1, Z40693.1, AI051759.1, AU022914.1, AI843362.1, G36524.1, AA459804.1, AI696320.1, AI051759.1, AI696214.1, AC010180.1, AA445859.1, AJ010949.1, AA190607.1, AI051759.1, T70594.1,T96901.1,AA766033.1, AI160471.1, AA719773.1, AI003601.1, AA442451.1, AA521470.1, AA770076.1, AA001411.1, AA001473.1, W22650.1, H86016.1, AC005342.1, AC005343.1, T96900.1, AI457823.1, AI377638.1, and AI433691.1, AA001473.1 and any of the polynucleotide sequences of SEQ ID NOS 1-16, 18-41, or 43-49.

32. The method of claim 31 wherein the disease is selected from the group consisting essentially of: seizure-related syndromes, migraine, ataxia, vestibular defects, chronic pain, mood, sleep interference,anxiety, ALS, multiple sclerosis,

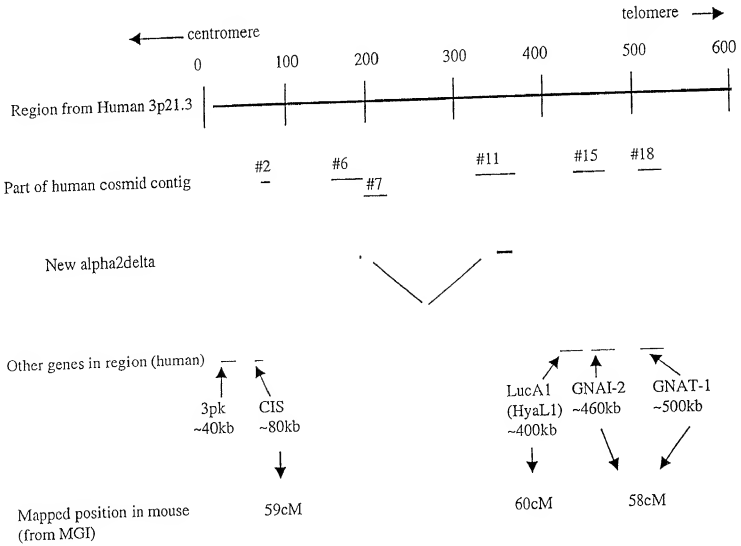
mania, tremor, parkinsonism, substance abuse/addiction syndromes, mood, depression, and cancer.

33. A method of using polynucleotide sequences to test for presence of a disease, or susceptibility to a disease, due to alterations or deletions in α2δ-C and/or α2δ-D, wherein the polynucleotide sequences are selected from the group consisting essentially of: M76559.1, AF040709.1, AF042792.1, AF042793.1, AB011130.1, T80372.1, AA360556.1, AI563965.1, N53512.1, AA000341.1, CAA90091.1, AI027237.1, AI026646.1, AA994701.1, AA887514.1, AI275868.1, AI675521.1, AA906993.1, AA301068.1, AI884536.1, AI862563.1, AI191453.1, AI241832.1, AA534927.1, AA329137.1, AI586961.1, AA394008.1, AW007700.1, R38827.1, AA255807.1, H11152.1, R60736.1, T16903.1, AA435601.1, AI094263.1, AA008996.1, AI105056.1, AI502878.1, Z84493.1, Z84494.1, Z75743.1, Z75742.1, Z84492.1, AA815447.1, AA190607.1, AI223142.1, AA188635.1, R43629.1, R20288.1, AA459684.1, AA662058.1, Z44942.1, Z40693.1, AI051759.1, AU022914.1, AI843362.1, G36524.1, AA459804.1, AI696320.1, AI051759.1, AI696214.1, AC010180.1, AA445859.1, AJ010949.1, AA190607.1, AI051759.1, T70594.1,T96901.1,AA766033.1, AI160471.1, AA719773.1, AI003601.1, AA442451.1, AA521470.1, AA770076.1, AA001411.1, AA001473.1, W22650.1, H86016.1, AC005342.1, AC005343.1, T96900.1, AI457823.1, AI377638.1, and AI433691.1, AA001473.1 and any of the polynucleotide sequences of SEQ ID NOS 1-16, 18-41, or 43-49.

34. A method of using polynucleotide sequences to identify the binding potential of the polynucleotide sequences to gabapentin, wherein the polynucleotide sequences are selected from the group consisting essentially of: M76559.1, AF040709.1, AF042792.1, AF042793.1, AB011130.1, T80372.1, AA360556.1, AI563965.1, N53512.1, AA000341.1, CAA90091.1, AI027237.1, AI026646.1, AA994701.1, AA887514.1, AI275868.1, AI675521.1, AA906993.1, AA301068.1, AI884536.1, AI862563.1, AI191453.1, AI241832.1, AA534927.1, AA329137.1, AI586961.1, AA394008.1, AW007700.1, R38827.1, AA255807.1, H11152.1, R60736.1, T16903.1, AA435601.1, AI094263.1, AA008996.1,

AI105056.1, AI502878.1, Z84493.1, Z84494.1, Z75743.1, Z75742.1, Z84492.1, AA815447.1, AA190607.1, AI223142.1, AA188635.1, R43629.1, R20288.1, AA459684.1, AA662058.1, Z44942.1, Z40693.1, AI051759.1, AU022914.1, AI843362.1, G36524.1, AA459804.1, AI696320.1, AI051759.1, AI696214.1, AC010180.1, AA445859.1, AJ010949.1, AA190607.1, AI051759.1, T70594.1,T96901.1,AA766033.1, AI160471.1, AA719773.1, AI003601.1, AA442451.1, AA521470.1, AA770076.1, AA001411.1, AA001473.1, W22650.1, H86016.1, AC005342.1, AC005343.1, T96900.1, AI457823.1, AI377638.1, and AI433691.1, AA001473.1 and any of the polynucleotide sequences of SEQ ID NOS 1-16, 18-41, or 43-49.

Fine Mapping of Alpha2/delta to mouse chromosome 9



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PCT/US99/23519

FIGURE #1 1/4

FIGURE #2

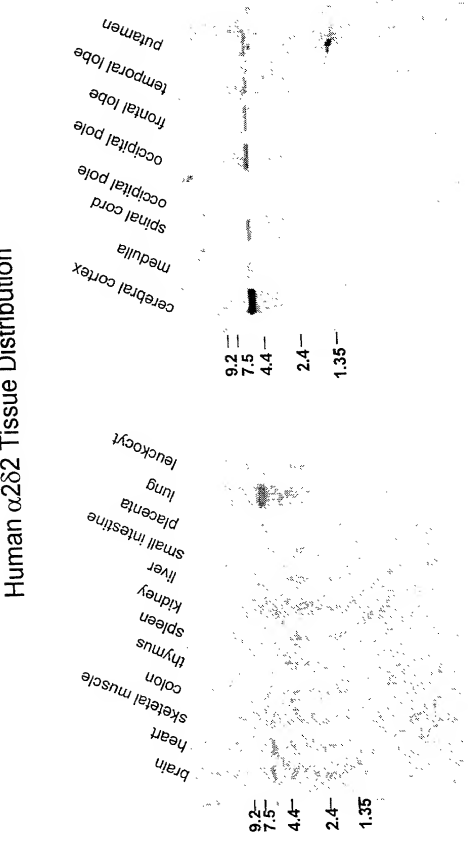
Human α2δ2 Tissue Distribution
brain
heart
skeletal muscle
colon
thymus
spleen
kidney
liver
small intestine
placenta
lung
leukocyt
cerebral cortex
medulla
spinal cord
occipital pole
occipital pole
frontal lobe
temporal lobe
putamen
9.2
7.5
4.4
2.4
1.35

Figure 3. [^{3}H] Gabapentin binding activity by human $\alpha 2\delta 2$ in transient ly transfected Cos 7 cells

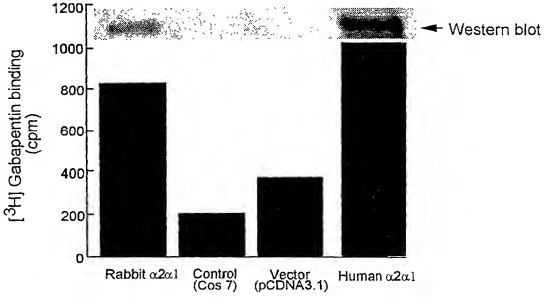

FIGURE #4

Lane 1-Brain RNA

Lane 2-Kidney RNA

Lane 3-Testis RNA

Lane 4-Lung RNA

Lane 5-Heart RNA

Lane 6-Placenta RNA

Lane 7-Liver RNA

Docket No.
5947-01-DRK

Declaration and Power of Attorney For Patent Application

English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

CALCIUM CHANNEL ALPHA-2/DELTA GENE

the specification of which

(check one)

☒ is attached hereto.

☐ was filed on _____ as United States Application No. or PCT International Application Number _____

and was amended on _____
(if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)			Priority Not Claimed
(Number)	(Country)	(Day/Month/Year Filed)	☐
(Number)	(Country)	(Day/Month/Year Filed)	☐
(Number)	(Country)	(Day/Month/Year Filed)	☐

I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

60/103,322	**10/7/98**
(Application Serial No.)	(Filing Date)
60/106,473	**10/30/98**
(Application Serial No.)	(Filing Date)
60/114,088	**12/29/98**
(Application Serial No.)	(Filing Date)

I hereby claim the benefit under 35 U. S. C. Section 120 of any United States application(s), or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. Section 112, I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, C. F. R., Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

PCT/US99/23519	**10/7/99**	**Pending**
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. *(list name and registration number)*

M. Andrea Ryan	**28,649**	**Jean Barish**	**34,118**
Charles W. Almer	**36,731**	**Todd M. Crissey**	**37,807**
Elizabeth M. Anderson	**31,585**	**Evan J. Federman**	**37,060**
Charles W. Ashbrook	**27,610**	**Evelyn D. Shen**	**39,834**
Michael J. Atkins	**35,431**	**Francis J. Tinney**	**33,069**
David R. Kurlandsky	41,505	**Linda A. Vag**	**32,071**
Claude F. Purchase, Jr.	P-47,871	Darryl C. Little	40,703
Suzanne M. Harvey	42,640	J. Trevor Lumb	28,567

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Sole or first inventor's signature — Date
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Full name of fourth inventor, if any
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Fourth inventor's signature

Date

Residence

Citizenship

Post Office Address

Full name of fifth inventor, if any
Not Applicable

Fifth inventor's signature

Date

Residence

Citizenship

Post Office Address

Full name of sixth inventor, if any
Not applicable

Sixth inventor's signature

Date

Residence

Citizenship

Post Office Address

SEQUENCE LISTING
(1) GENERAL INFORMATION:

(i) APPLICANT:
(A) NAME: Margaret Ann Johns
(B) STREET:
(C) CITY:
(D) STATE:
(E) COUNTRY:
(F) POSTAL CODE (ZIP):
(G) TELEPHONE:
(H) TELEFAX:

APPLICANT:
(A) NAME: Brian Jay Moldover
(B) STREET:
(C) CITY:
(D) STATE:
(E) COUNTRY:
(F) POSTAL CODE (ZIP):
(G) TELEPHONE:
(H) TELEFAX:

APPLICANT:
(A) NAME: James David Offord
(B) STREET:
(C) CITY:
(D) STATE:
(E) COUNTRY:
(F) POSTAL CODE (ZIP):
(G) TELEPHONE:
(H) TELEFAX:

(ii) TITLE OF INVENTION: Alpha-2/Delta Gene

(iii) NUMBER OF SEQUENCES: 49

(iv) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30 (EPO)

(2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH:
(B) TYPE:
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

(A) NAME/KEY: Coding Sequence

(B) LOCATION:

(D) OTHER INFORMATION: α2δ-B

(iii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

GGGGCAGCGCAGAGAGGCGCTGCGGCCCGTGCAGACCCCGGAGGCCCCTCGCGGAGAAGGCG
GCGGCGGAGGAGAGGCCGAGTTACCGCCCCCCCCCCGCGCCCCCCCAACCCCGCCGCCGCCGCC
CGCCGCCACTGCCCCCCCTCCCCGCGGCGCCGCATCTTGAATGGAAACATGGCGGTGCCGGCTCGG
ACCTGCGGCGCCTCTCGGCCCGGCCCAGCGCGGACTGCGCGCCCCTGGCCCGGCTGCGGCCCCCAC
CCTGGCCCCGGCACCCGGCGCCCGACGTCCGGGCCCCCGCGCCCGCTGTGGCTGCTGCTGCCGCTT
CTACCGCTGCTCGCCGCCCCGGCGCCTCTGCCTACAGCTTCCCCCAGCAGCACACGATGCAGCAC
TGGGCCCGGCGTCTGGAGCAGGAGGTCGACGGCGTGATGCGGATTTTTGGAGGCGTCCAGCAGCTC
CGTGAGATTTACAAGGACAACCGGAACCTGTTCGAGGTACAGGAGAATGAGCCTCAGAAGTTGGTG
GAGAAGGTGGCAGGGGACATTGAGAGCCTTCTGGACAGGAAGGTGCAGGCCCTGAAGAGACTGGCT
GATGCTGCAGAGAACTTCCAGAAAGCACACCGCTGGCAGGACAACATCAAGGAGGAAGACATCGTG
TACTATGACGCCAAGGCTGACGCTGAGCTGGACGACCCTGAGAGTGAGGATGTGGAAAGGGGGTCT
AAGGCCAGCACCCTAAGGCTGGACTTCATCGAGGACCCAAACTTCAAGAACAAGGTCAACTATTCA
TACGCGGCTGTACAGATCCCTACGGACATCTACAAAGGCTCCACTGTCATCCTCAATGAGCTCAAC
TGGACAGAGGCCCTGGAGAATGTGTTCATGGAAAACCGCAGACAAGACCCCACACTGCTGTGGCAG
GTCTTCGGCAGCGCCACAGGAGTCACTCGCTACTACCCGGCCACCCCGTGGCGAGCCCCCAAGAAG
ATCGACCTGTACGATGTCCGAAGGAGACCCTGGTATATCCAGGGGGCCTCGTCACCCAAAGACATG
GTCATCATCGTGGATGTGAGTGGCAGTGTGAGCGGCCTGACCCTGAAGCTGATGAAGACATCTGTC
TGCGAGATGCTGGACACGCTGTCTGATGATGACTATGTGAATGTGGCCTCGTTCAACGAGAAGGCA
CAGCCTGTGTCATGCTTCACACACCTGGTGCAGGCCAATGTGCGCAACAAGAAGGTGTTCAAGGAA
GCTGTGCAGGGCATGGTGGCCAAGGGCACCACAGGCTACAAGGCCGGCTTTGAGTATGCCTTTGAC
CAGCTGCAGAACTCCAACATCACTCGGGCCAACTGCAACAAGATGATCATGATGTTCACGGATGGT
GGTGAGGACCGCGTGCAGGACGTCTTTGAGAAGTACAATTGGCCAAACCGGACGGTGCGCGTGTTT
ACTTTCTCCGTGGGGCAGCATAACTATGACGTCACACCGCTGCAGTGGATGGCCTGTGCCAACAAA
GGCTACTATTTTGAGATCCCTTCCATCGGAGCCATCCGCATCAACACACAGGAATATCTAGATGTG
TTGGGCAGGCCCATGGTGCTGGCAGGCAAGGAGGCCAAGCAGGTTCAGTGGACCAACGTGTATGAG
GATGCACTGGGACTGGGGTTGGTGGTAACAGGGACCCTCCCTGTTTTCAACCTGACACAGGATGGC
CCTGGGGAAAAGAAGAACCAGCTGATCCTGGGCGTGATGGGCATTGACGTGGCTCTGAATGACATC
AAGAGGCTGACCCCCAACTACACGCTTGGAGCCAACGGCTATGTGTTTGCCATTGACCTGAACGGC
TACGTGTTGCTGCACCCCAATCTCAAGCCCCAGACCACCAACTTCCGGGAGCCTGTGACTCTGGAC
TTCCTGGATGCGGAGCTAGAGGATGAGAACAAGGAAGAGATCCGTCGGAGCATGATTGATGGCAAC
AAGGGCCACAAGCAGATCAGAACGTTGGTCAAGTCCCTGGATGAGAGGTACATAGATGAGGTGACA
CGGAACTACACCTGGGTGCCTATAAGGAGCACTAACTACAGCCTGGGGCTGGTGCTCCCACCCTAC
AGCACCTTCTACCTCCAAGCCAATCTCAGTGACCAGATCCTGCAGGTCAAGTATTTTGAGTTCCTG
CTCCCCAGCAGCTTTGAGTCTGAAGGACACGTTTTCATTGCTCCCAGAGAGTACTGCAAGGACCTG
AATGCCTCAGACAACAACACCGAGTTCCTGAAAAACTTTATTGAGCTCATGGAGAAAGTGACTCCA
GACTCCAAGCAGTGCAACAACTTCCTTCTGCACAACCTGATCTTGGACACGGGCATCACGCAGCAG
CTGGTAGAGCGTGTGTGGAGGGACCAGGATCTCAACACGTACAGCCTACTGGCCGTGTTCGCTGCC
ATCAGACGGTGGCATCACCCGAGTCTTCCCCAACAAGGCAGCTGAGGACTGGACAGAGAACCCTGAG
CCCTTCAATGCCAGCTTCTACCGCCGCAGCCTGGATAACCACGGTTATGTCTTCAAGCCCCCACAC
CAGGATGCCCTGTTAAGGCGCTGGAGCTGGAGAATGACACTGTGGGCATCCTCGTCAGCACAGCT
GTGGAGCTCAGCCTAGGCAGGCGCACACTGAGGCCAGCAGTGGTGGGCGTCAAGCTGGACCTAGAG
GCTTGGGCTGAGAAGTTCAAGGTGCTAGCCAGCAACCGTACCCACCAAGACCAGCCTCAGAAGTGC
GGCCCCAACAGCCACTGTGAGATGGACTGCGAGGTTAACAATGAGGACTTACTCTGTGTCCTCATT
GATGATGGAGGATTCCTGGTGCTGTCAAACCAGAACCATCAGTGGGACCAGGTGGGCAGGTTCTTC
AGTGAGGTGGATGCCAACCTGATGCTGGCACTCTACAATAACTCCTTCTACACCCGCAAGGAGTCC
TATGACTATCAGGCAGCCTGTGCCCCTCAGCCCCCTGGCAACCTGGGTGCTGCACCCCGGGGTGTC
TTTGTGCCCACCGTTGCAGATTTCCTTAACCTGGCCTGGTGGACCTCTGCTGCCGCCTGGTCCCTG
TTCCAGCAGCTTCTCTACGGCCTCATCTACCACAGCTGGTTCCAAGCAGACCCCGCGGAGGCCGAG
GGGAGCCCCGAGACGCGCGAGAGCAGCTGCGTCATGAAACAGACCCAGTACTACTTCGGCTCGGTA
AACGCCTCCTACAACGCCATCATCGACTGCGGAAACTGCTCCAGGCTGTTCCACGCGCAGAGACTG
ACCAACACCAATCTTCTCTTTGTGGTGGCCGAGAAGCCGCTGTGCAGCCAGTGCGAGGCTGGCCGG
CTGCTGCAGAAGGAGACGCACTGCCCAGCGGACGGCCCGGAGCAGTGTGAGCTAGTGCAGAGACCG
CGATACCGGAGAGGCCCGCACATCTGCTTCGACTACAACGCGACAGAAGATACCTCAGACTGTGGC
CGCGGGGCCTCCTTCCCGCCGTCGCTGGGCGTCCTGGTCTCCCTGCAACTGCTGCTCCTCCTGGGC
CTGCCGCCCCGGCCGCAGCCTCAAGTCCTCGTCCACGCCTCTCGCCGCCTCTGAGCACCCTGCCCC
ACCCCACCTCCACTCCCACCTCACCCGCCTCTTCGCCTTTCCCACCCTCCTGCCCCACACTCCCC
GCCTTAGAGCCTCGTCCCTCCCTCACTGAAGGACCTGAGCTGGCCAGGCCCTGAGAGTCTGGTCTG

CGCCTTGGGATGGGGAGTCCCAAAGCGGGACGCCGCAGGTGTTTGGCACCCAAATCACATCTCACC
TCCGAACTGTTCAAGTGTCCCCAGACCCTTCTTGCCTGCTGGGCTCCCCCCAGTGGGATGGGACAG
GGAGGCCACACGCACTGGTGCCAAAACCAGGCCTCTGCTGCCGCCCTTCCTGGAGGCTGCCTATGT
TGGGGGGGACCCTGCCTCAGCTGACCCGGCCTCTCTGCCCCACCCAAGCCCAAACTTGGTTTCTGT
GAGAATAGTGGAGGAAGGTGAGATGGCCAGTTTGAAGCCTGTGCCTCCCAGCTTAAATCCTAGCAG
GAGAGAGGCTCTGGGGCAGCCCCCATGGGCTCCTGCCCCTTTCAGGCCTACAGCCACATCCCCAAG
CCCACCAGGTGTCAGGATAGTCACAGTGATACCAGTTCAGACACTACCCATATACACCTGGAACA
TTGAGGATGGAAACTGGACTCACATTCGACATACCCCACTGGGCACACGCACAAACACACACACTA
TGGGGTGGGGTGGGTGTAGGGGCTTACAAAGCCTTACACAGGGCGAGGGGTTGGTGGGAGGGTTGG
CACCTGCACACTCCATCTCCTGCTCACCACCTGCCTCTAATCTGAGCTGCAGCCTGGCTGGTCCTC
CCATTTCTAAAGCTGAATGTCAAACAGTGCCAAATGCTGGGGCAGGGGGTGAAGAACCCTCTGTCC
CACCCCTAGCCACCAGTGTCCTCCAAGTGCCCCCTCACCTCTCCAGGTGCTCATTGTAACCATTTC
TCACTAGTGTCAGGCCCCCAGTGGGACCACATGCCACTGCCTGCCACCTTTCGGCAGAGGAACCCCC
ACCAGACATCACCCTTTGCCTTAGCAGGGGTGACTTTGTCTCTCCTGGCTGGGCCATCCTTCCGCC
AATCTGGCCCTTACACACTCAGGCCTGTGCCCACTCCCTATCTCCTTCCCACCCCTACACACACAC
TCCCTGCTTGCAGGAGGCCAAACTGTCCCTCCCTTGCTGAACACACACACACACACACACACACAG
GTGGGGACTGGGCACAGCTCTTCACACCATTCATTCTGGTCATTTCCCCCAAAGGCATCCCAGCCT
GGGGGCCAGTGGGGAACTGAGGGCAAGGGGATATAGTGATGGGGCTCAGATGGACTGGGAGGAGGG
GGAGGGTGATGCATTAATTAATGGCTTCGTTAATTAATGTCATGTTGCTTGTCGCTTTCTCAGTGT
GTGTGTTGTGGTCCATGCCCACTGCTGGTGCCAGGGTGGGTGTCCATGTGCACCCGGCCTGGATGCC
AGCTGTGTCCTTCGGGGGCGTGCGTGTAACTGTAGTGTAGTCAGGTGCTCAATGGAGAATATAAAC
ATATACAGAAAAATATATATTTTAAGTTTAAAAAACAGAAAAACAGACAAAACAATCCCCATCAGG
TAGCTGTCTAACCCCCAGCTGGGTCTAATCCTTCTCATTACCCACCCGACCTGGCTGCCCCTCACC
TTGGGCTGGGGGACTGGGGGGCCATTTCCTTTTCTCTGCCCTTTTTTTGTTGTTCTATTTTGTACA
GACAAGTTGGAAAAACAACAGCGACAAAAAAGTCAAGAAACTTTGTAAAATATCGTGTGTGTGATT
CCTTGTAAAATATTTTCAAATGGTTTATTACAGAAGATCAGTTATTAAATAATGTTCATATTTTCA
CTTC

(2) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH:
(B) TYPE:
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(ix) FEATURE:

(A) NAME/KEY: Coding Sequence

(B) LOCATION:

(D) OTHER INFORMATION: α2δ-B

(iii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

MAVPARTCGASRPGPARTARPWPGCGPHPGPGTRRPTSGPPRPLWLLLPLLPLLAAPGASAYSFPQ
QHTMQHWARRLEQEVDGVMRIFGGVQQLREIYKDNRNLFEVQENEPQKLVEKVAGDIESLLDRKVQ
ALKRLADAAENFQKAHRWQDNIKEEDIVYYDAKADAELDDPSESDVERGSKASTLRLDFIEDPNFK
NKVNYSYAAVQIPTDIYKGSTVILNELNWTEALENVFMENRRQDPTLLWQVFGSATGVTRYYPATP
WRAPKKIDLYDVRRRPWYIQGASSPKDMVIIVDVSGSVSGLTLKLMKTSVCEMLDTLSDDDYVNVA
SFNEKAQPVSCFTHLVQANVRNKKVFKEAVQGMVAKGTTGYKAGFEYAFDQLQNSNITRANCNKMI
MMFTDGGEDRVQDVFEKYNWPNRTVRVFTFSVGQHNYDVTPLQWMACANKGYYFEIPSIGAIRINT
QEYLDVLGRPMVLAGKEAKQVQWTNVYEDALGLGLVVTGTLPVFNLTQDGPGEKKNQLILGVMGID
VALNDIKRLTPNYTLGANGYVFAIDLNGYVLLHPNLKPQTTNFREPVTLDFLDAELEDENKEEIRR
SMIDGNKGHKQIRTLVKSLDERYIDEVTRNYTWVPIRSTNYSLGLVLPPYSTFYLQANLSDQILQV
KYFEFLLPSSFESEGHVFIAPREYCKDLNASDNNTEFLKNFIELMEKVTPDSKQCNNFLLHNLILD
TGITQQLVERVWRDQDLNTYSLLAVFAATDGGITRVFPNKAAEDWTENPEPFNASFYRRSLDNHGV
VFKPPHQDALLRPLELENDTVGILVSTAVELSLGRRTLRPAVVGVKLDLEAWAEKFKVLASNRTHQ

DQPQKCGPNSHCEMDCEVNNEDLLCVLIDDGGFLVLSNQNHQWDQVGRFFSEVDANLMLALYNNSF
YTRKESYDYQAACAPQPPGNLGAAPRGVFVPTVADFLNLAWWTSAAAWSLFQQLLYGLIYHSWFQA
DPAEAEGSPETRESSCVMKQTQYYFGSVNASYNAIIDCGNCSRLFHAQRLTNTNLLFVVAEKPLCS
QCEAGRLLQKETHCPADGPEQCELVQRPRYRRGPHICFDYNATEDTSDCGRGASFPPSLGVLVSLQ
LLLLLGLPPRPQPQVLVHASRRL

(2) INFORMATION FOR SEQ ID NO: 3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH:
(B) TYPE:
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

(A) NAME/KEY: Coding Sequence

(B) LOCATION:

(D) OTHER INFORMATION: α2δ-C

(iii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

TACTATAGGGCGGCCGCGAATTCGGCACGAGGCGGCGCGGAGCGGAGCAGGCAGCCCCGCGCGCTC
GCCCACCGCCCGCTCCGCGCAGCTCCCCGCGGCCGCTCTCGTCGCCGCCGCAGCGGGCGCGTCGGA
GGGAGCCCAGCATGGCCGGGCCGGGCTCGCCGCGCCGCGCGTCCCGGGGGGCCTCGGCGCTTCTCG
CTGCCGCGCTTCTCTACGCCGCGTGGGGGACGTGGTGCGCTCGGAGCAGCAGATACCGCTCTCCG
TGGTGAAGCTCTGGGCCTCGGCTTTTGGTGGGGAGATAAAATCCATTGCTGCTAAGTACTCCGGTT
CCCAGCTTCTGCAAAAGAAATACAAAGAGTATGAGAAAGACGTTGCCATAGAAGAAATTGATGGCC
TCCAACTGGTAAAGAAGCTGGCAAAGAACATGGAAGAGATGTTTCACAAGAAGTCTGAGGCCGTCA
GGCGTCTGGTGGAGGCTGCAGAAGAAGCACACCTGAAACATGAATTTGATGCAGACTTACAGTATG
AATACTTCAATGCTGTGCTGATAAATGAAAGGGACAAAGACGGGAATTTTTTGGAGCTGGGAAAGG
AATTCATCTTAGCCCCAAATGACCATTTTAATAATTTGCCTGTGAACATCAGTCTAAGTGACGTCC
AAGTACCAACGAACATGTACAACAAAGACCCTGCAATTGTCAATGGGGTTTATTGGTCTGAATCTC
TAAACAAAGTTTTTGTAGATAACTTTGACCGTGACCCATCTCTCATATGGCAGTACTTTGGAAGTG
CAAAGGGCTTTTTTAGGCAGTATCCGGGGATTAAATGGGAACCAGATGAGAATGGAGTCATTGCCT
TCGACTGCAGGAACCGAAAATGGTACATCCAGGCAGCAACTTCTCCGAAAGACGTGGTCATTTTAG
TTGACGTCAGTGGCAGCATGAAAGGACTCCGTCTGACTATCGCGAAGCAAACAGTCTCATCCATTT
TGGATACACTTGGGGATGATGACTTCTTCAACATAATTGCTTATAATGAGGAGCTTCACTATGTGG
AACCTTGCCTGAATGGAACTTTGGTGCAAGCCGACAGGACAAACAAAGAGCACTTCAGGGAGCATC
TGGACAAACTTTTCGCCAAAGGAATTGGAATGTTGGATATAGCTCTGAATGAGGCCTTCAACATTC
TGAGTGATTTCAACCACACGGGACAAGGAAGTATCTGCAGTCAGGCCATCATGCTCATAACTGATG
GGGCGGTGGACACCTATGATACAATCTTTGCAAAATACAATTGGCCAGATCGAAAGGTTCGCATCT
TCACATACCTCATTGGACGAGAGGCTGCGTTTGCAGACAATCTAAAGTGGATGGCCTGTGCCAACA
AAGGATTTTTTACCCAGATCTCCACCTTGGCTGATGTGCAGGAGAATGTCATGGAATACCTTCACG
TGCTTAGCCGGCCCAAAGTCATCGACCAGGAGCATGATGTGGTGTGGACCGAAGCTTACATTGACA
GCACTCTGACTGATGATCAGGGCCCCGTCCTGATGACCACTGTAGCCATGCCTGTGTTTAGTAAGC
AGAACGAAACCAGATCGAAGGGCATTCTTCTGGGAGTGGTTGGCACAGATGTCCCAGTGAAAGAAC
TTCTGAAGACCATCCCAAATACAAGTTAGGGATTCACGGTTATGCCTTTGCAATCACAAATAATG
GRTATATCCTGACGCATCCGGAACTCAGGCTGCTGTACGAAGAAGGAAAAAAGCGAAGGAAACCTA
ACTATAGTAGCGTTGACCTCTCTGAGGTGGAGTGGGAAGACCGAGATGACGTGTTGAGAAATGCTA
TGGTGAATCGAAAGACGGGGAAGTTTTCCATGGAGGTGAAGAAGACAGTGGACAAAGGGAAACGGG
TTTTGGTGATGACAAATGACTACTATTATACAGACATCAAGGGTACTCCTTTCAGTTTAGGTGTGG
CGCTTTCCAGAGGTCATGGGAAATATTTCTTCCGAGGGAATGTAACCATCGAAGAAGGCCTGCATG
ACTTAGAACATCCCGATGTGTCCTTGGCAGATGAATGGTCCTACTGCAACACTGACCTACACCCTG
AGCACCGCCATCTGTCTCAGTTAGAAGCGATTAAGCTCTACCTAAAAGGCAAAGAACCTCTGCTCC
AGTGTGATAAAGAATTGATCCAAGAAGTCCTTTTTGACGCGGTGGTGAGTGCCCCATTGAAGCGT
ATTGGACCAGCCTGGCCCTCAACAAATCTGAAAATTCTGACAAGGGCGTGGAGGTTGCCTTCCTCG

GCACTCGCACGGGCCTCTCCAGAATCAACCTGTTTGTCGGGGCTGAGCAGCTCACCAATCAGGACT
TCCTGAAAGCTGGCGACAAGGAGAACATTTTTAACGCAGACCATTTCCCTCTCTGGTACCGAAGAG
CCGGCTGAGCAGATTCCAGGGAGCTTCGTCTACTCGATCCCATTCAGCACTGGACCAGTCAATAAAA
GCAATGTGGTGACAGCAAGTACATCCATCCAGCTCCTGGATGAACGGAAATCTCCTGTGGTGGCAG
CTGTAGGCATTCAGATGAAACTTGAATTTTTCCAAAGGAAGTTCTGGACTGCCAGCAGACAGTGTG
CTTCCCTGGATGGCAAATGCTCCATCAGCTGTGATGATGAGACTGTGAATTGTTACCTCATAGACA
ATAATGGATTATTTGGTGTCTGAAGACTACACACAGACTGGAGACTTTTTGGTGAGATCGAGG
GAGCTGTGATGAACAAATTGCTAACAATGGGCTCCTTTAAAAGAATTACCCTTTATGACTACCAAG
CCATGTGTAGAGCCAACAAGGAAAGCAGCGATGGCGCCCATGGCCTCCTGGATCCTTATAATGCCT
TCCTCTCTGCAGTAAAATGGATCATGACAGAACTTGTCTTGTTCCTGGTGGAATTTAACCTCTGCA
GTTGGTGGCACTCCGATATGACAGCTAAAGCCCAGAAATTGAAACAGACCCTGGAGCCTTGTGATA
CTGAATATCCAGCATTCGTCTCTGAGCGCACCATCAAGGAGACTACAGGGAATATTGCTTGTGAAG
ACTGCTCCAAGTCCTTTGTCATCCAGCAAATCCCAAGCAGCAACCTGTTCATGGTGGTGGTGGACA
GCAGCTGCCTCTGTGAATCTGTGGCCCCCATCACCATGGCACCCATTGAAATCAGGTATAATGAAT
CCCTTAAGTGTGAACGTCTAAAGGCCCAGAAGATCAGAAGGCGCCCAGAATCTTGTCATGGCTTCC
ATCCTGAGGAGAATGCAAGGGAGTGTGGGGGTGCGCCGAGTCTCCAAGCCCAGACAGTCCTCCTTC
TGCTCCCTCTGCTTTTGATGCTCTTCTCAAGGTGACACTGACTGAGATGTTCTCTTACTGACTGAG
ATGTTCTCTTGGCATGCTAAATCATGGATAAACTGTGAACCAAAATATGGTGCAACATACGAGACA
TGAATATAGTCCAACCATCAGCATCTCATCATGATTTTAAACTGTGCGTGATATAAACTCTTAAAG
ATATGTTGACAAAAAGTTATCTATCATCTTTTTACTTTGCCAGTCATGCAAATGTGAGTTTGCCAC
ATGATAATCACCCTTCATCAGAAATGGGACCGCAAGTGGTAGGCAGTGTCCCTTCTGCTTGAAACC
TATTGAAACCAATTTAAAACTGTGTACTTTTTAAATAAAGTATATTAAAATCATAAAAAAAAAAAA
AAAAAAAA

(2) INFORMATION FOR SEQ ID NO: 4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH:
(B) TYPE:
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:

(A) NAME/KEY: Coding Sequence

(B) LOCATION:

(D) OTHER INFORMATION: α2δ-D

(iii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

CCATGCCTGCAACTCCCAACTTCCTCGCAAACCCCAGCTCCAGCAGCCGCTGGATTCCCCTCCAGC
CAATGCCCGTGGCCTGGGCCTTTGTGCAGAAGACCTCGGCCCTCCTGTGGCTGCTGCTTCTAGGCA
CCTCCCTGTCCCCTGCGTGGGGACAGGCCAAGATTCCTCTGGAAACAGTGAAGCTATGGGCTGACA
CCTTCGGCGGGGACCTGTATAACACTGTGACCAAATACTCAGGCTCTCTCTTGCTGCAGAAGAAGT
ACAAGGATGTGGAGTCCAGTCTGAAGATCGAGGAGGTGGATGGCTTGGAGCTGGTGAGGAAGTTCT
CAGAGGACATGGAGAACATGCTGCGGAGGAAAGTCGAGGCGGTCCAGAATCTGGTGGAAGCTGCCG
AGGAGGCCGACCTGAACCACGAATTCAATGAATCCCTGGTGTTCGACTATTACAACTCGGTCCTGA
TCAACGAGAGGGACGAGAAGGGCAACTTCGTGGAGCTGGGCGCCGAGTTCCTCCTGGAGTCCAATG
CTCACTTCAGCAACCTGCCGGTGAACACCTCCATCAGCAGCGTGCAGCTGCCCACCAACGTGTACA
ACAAAGACCCAGATATTTAAATGGAGTCTACATGTCTGAAGCCTTGAATGCTGTCTTCGTGGAGA
ACTTCCAGAGAGACCCAACGTTGACCTGGCAATATTTTGGCAGTGCAACTGGATTCTTCAGGATCT
ATCCAGGTATAAAATGGACACCTGATGAGAATGGAGTCATTACTTTTGACTGCCGAAACCGCGGCT
GGTACATTCAAGCTGCTACTTCTCCCAAGGACATAGTGATTTTGGTGGACGTGAGCGGCAGTATGA
AGGGGCTGAGGATGACTATTGCCAAGCACACCATCACCACCATCTTGGACACCCTGGGGGAGAATG
ACTTCGTTAATATCATAGCGTACAATGACTACGTCCATTACATCGAGCCTTGTTTTAAAGGGATCC
TCGTCCAGGCGGACCGAGACAATCGAGAGCATTTCAAACTGCTGGTGGAGGAGTTGATGGTCAAAG

GTGTGGGGGTCGTGGACCAAGCCCTGAGAGAAGCCTTCCAGATCCTGAAGCAGTTCCAAGAGGCCA
AGCAAGGAAGCCTCTGCAACCAGGCCATCATGCTCATCAGCGACGGCGCCGTGGAGGACTACGAGC
CGGTGTTTGAGAAGTATAACTGGCCAGACTGTAAGGTCCGAGTTTTCACTTACCTCATTGGGAGAG
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TCAACCACGACCACGACATCATCTGGACAGAGGCCTACATGGACAGCAAGCTCCTCAGCTCGCAGG
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AAACAGGTACTCTCTCGATGGATGTGAAGGTTCCGATGGATAAAGGGAAGCGAGTTCTTTTCCTGA
CCAATGACTACTTCTTCACGGACATCAGCGACACCCCTTTCAGTTTGGGGGTGGTGCTGTCCCGGG
GCCACGGAGAATACATCCTTCTGGGGAACACGTCTGTGGAAGAAGGCCTGCATGACTTGCTTCACC
CAGACCTGGCCCTGGCCGGTGACTGGATCTACTGCATCACAGATATTGACCCAGACCACCGGAAGC
TCAGCCAGCTAGAGGCCATGATCCGCTTCCTCACCAGGAAGGACCCAGACCTGGAGTGTGACGAGG
AGCTGGTCCGGGAGGTGCTGTTTGACGCGGTGGTGACAGCCCCCATGGAAGCCTACTGGACAGCGC
TGGCCCTCAACATGTCCGAGGAGTCTGAACACGTGGTGGACATGGCCTTCCTGGGCACCCGGGCTG
GCCTCCTGAGAAGCAGCTTGTTCGTGGGCTCCGAGAAGGTCTCCGACAGGAAGTTCCTGACACCTG
AGGACGAGGCCAGCGTGTTCACCCTGGACCGCTTCCCGCTGTGGTACCGCCAGGCCTCAGAGCATC
CTGCTGGCAGCTTCGTCTTCAACCTCCGCTGGGCAGAAGGACCAGAAAGTGCGGGTGAACCCATGG
TGGTGACGGCAAGCACAGCTGTGGCGGTGACCGTGGACAAGAGGACAGCCATTGCTGCAGCCGCGG
GCGTCCAAATGAAGCTGGAATTCCTCCAGCGCAAATTCTGGGCGGCAACGCGGCAGTGCAGCACTG
TGGATGGGCCGTGCACACAGAGCTGCGAGGACAGTGATCTGGACTGCTTCGTCATCGACAACAACG
GGTTCATTCTGATCTCCAAGAGGTCCCGAGAGACGGGAAGATTTCTGGGGGAGGTGGATGGTGCTG
TCCTGACCCAGCTGCTCAGCATGGGGGTGTTCAGCCAAGTGACTATGTATGACTATCAGGCCATGT
GCAAACCCTCGAGTCACCACCACAGTGCAGCCCAGCCCCTGGTCAGCCCAATTTCTGCCTTCTTGA
CGGCGACCAGGTGGCTGCTGCAGGAGCTGGTGCTGTTCCTGCTGGAGTGGAGTGTCTGGGGCTCCT
GGTACGACAGAGGGGCCGAGGCCAAAAGTGTCTTCCATCACTCCCACAAACACAAGAAGCAGGACC
CGCTGCAGCCCTGCGACACGGAGTACCCCGTGTTCGTGTACCAGCCGGCCATCCGGGAGGCCAACG
GGATCGTGGAGTGCGGGCCCTGCCAGAAGGTATTTGTGGTGCAGCAGATTCCCAACAGTAACCTCC
TCCTCCTGGTGACAGACCCCACCTGTGACTGCAGCATCTTCCCACCAGTGCTGCAGGAGGCGACAG
AAGTCAAATATAATGCCTCTGTCAAATGTGACCGGATGCGCTCCCAGAAGCTCCGCCGGCGACCAG
ACTCCTGCCACGCCTTCCATCCAGAGGAGAATGCCCAGGACTGCGGCGGCGCCTCGGACACCTCAG
CCTCGCCGCCCCTACTCCTGCTGCCTGTGTGTGCCTGGGGGCTACTGCCCCAACTCCTGCGGTGAC
ACCACCCAGCCTGACCTGTGTTTTGGCAAGGTGATCCTTCCAGAGCCATCCCAAAAAGTCAGCACT
GACATGGGATGCAGCTAACTGCAGTTGGGTCGCCCCCAGGCCAACGCTCCTCTCAATCCTGGGCTG
GTGGCCCCTGGCTCCGGAGAATGCTGGATGGAACAGGAAACCAATCACCTGGCACCACTTTCAAGA
TGCTTCATGGTGCCCGGTACCATCTGCCCTAGGTCTCAACATGAGCATACTTCTGACCTAACCTTC
CTGTCTCCTCTTCGGGAAGCCAGCGTGAGCTCAGCTTGGACCAAGACAAAATAATTTAGTTCTTCC
TGTACTCCAGAGTCCAGACCCAGCCAAGAAAGGGTCAGTTGTTTCTGACCCTTTCTGTCGGAGTGG
TCTCTGGTAGAACCCAAGGACTTCTGGGTACTGAGAAGCAGCAGCAGAATGAGGCCAAATGCAGAG
ATGAGGCTAAGGCAAGAATATGCCCCAACTAAAGCATAGATTCCCCAAAGTGAGGCTCATGGTGGG
AGGCCACTCACCTTCCTAGCTGCTGCTCGAAAAGGTTTTGACTGTGTTGGGGTGGGGGTTGGGTAA
GGGAATGGTCAAGACTGAGAAAGGAATGAAATCCATTCAGGAAATATCGACAGGGCTACACGTGAT
GTCCCCAAACTGCTGCTATTGAAGAACTTCCCAAAACTTCTTTACAAAGCCCTAAAGGAAAGTTTG
CATCTATGAAAAGCCAATAGGCTGAGACATCCAATTGCTGCATGGAAATTGATGTACATTCAGGGG
ACGGCAAAAATAGCTGTAAAATAGTGAAAAAGAGCAGTGGTTGTGCTCTTTTCTGGCCAATGATTT
ACAAAAGAATCTACTTGACTCTGTCCCTGGAGTGAAATCCTTAGGGTTGGAACTTGTGGGAACATT
CCAACTTGCTAAGCAGGGTCCACTGGGAGGGAAGCTCTATCTGGGAACTCACCCCCAGCGCACACA
CATCTCCCCCAGGGTCCCAAGGCCCCGCAGCTTCCTCCCCCGACCAAACCCCAAGACCTGGATCCC
AGGAGACAACAGTCTCCACATGAGAGCAACATTAAGGGCAAAGCCATGGAGAAATGTGGGAGAGGC
CGGCCTCAAATCTTTCCATTTAACAAACCCCAGTGATGGGTATGGACAGCATGCAGGGCTTTTGGG
GCGCTTCCCCCCGCTCCTCCATCACCCTCAGCCTCCACACTTCAAAGTTCAAGTTCAAAGCTGTTC
AAGTTTCCTACCAGCAAATAGCCCTAACTTGCCTCTAGAGTAGGCCAAATGCCAACTCTGTAAAAC
ACACTTACATTATCGGTTACAGAATGTCACTCTTACCATCATGTCTTGCAACAACCCTGTGAGGGC
AGTATTAATGCCCCCTTACAGCAGAAGACACTGCAGCTCGAAGACAGCTTAAGTGGCAGAATAATG
CTAGAACAGCTAAGGTTTACATGTACCAAATAACATGTTTCAGCTCATTCCATCCTCACAACAGCC
CCCTGAAAGTGGGTACTATCATTAGTCCCATGTTATAGAAACTGCAGCAGAGTTGAAAATTGCCTC

CAAATTACCGGAAGAGTGTATGAAGATTGAATGTGATGTATTCACGTAACATGCTTGAAACTGCCT
GGCATATACTAAACGCTAAATAAATACATGCTAACTGCAAAAAAAAAAAAAAAAAAA

(2) INFORMATION FOR SEQ ID NO: 5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH:
(B) TYPE:
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: protein

(ix) FEATURE:

(A) NAME/KEY:

(B) LOCATION:

(D) OTHER INFORMATION: α2δ-C

(iii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

MAGPGSPRRASRGASALLAAALLYAALGDVVRSEQQIPLSVVKLWASAFGGEIKSIAAKYSGSQLL
QKKYKEYEKDVAIEEIDGLQLVKKLAKNMEEMFHKKSEAVRRLVEAAEEAHLKHEFDADLQYEYFN
AVLINERDKDGNFLELGKEFILAPNDHFNNLPVNISLSDVQVPTNMYNKDPAIVNGVYWSESLNKV
FVDNFDRDPSLIWQYFGSAKGFFRQYPGIKWEPDENGVIAFDCRNRKWYIQAATSPKDVVILVDVS
GSMKGLRLTIAKQTVSSILDTLGDDDFFNIIAYNEELHYVEPCLNGTLVQADRTNKEHFREHLDKL
FAKGIGMLDIALNEAFNILSDFNHTGQGSICSQAIMLITDGAVDTYDTIFAKYNWPDRKVRIFTYL
IGREAAFADNLKWMACANKGFFTQISTLADVQENVMEYLHVLSRPKVIDQEHDVVWTEAYIDSTLT
DDQGPVLMTTVAMPVFSKQNETRSKGILLGVVGTDVPVKELLKTIPKYKLGIHGYAFAITNNGYIL
THPELRLLYEEGKKRRKPNYSSVDLSEVEWEDRDDVLRNAMVNRKTGKFSMEVKKTVDKGKRVLVM
TNDYYYTDIKGTPFSLGVALSRGHGKYFFRGNVTIEEGLHDLEHPDVSLADEWSYCNTDLHPEHRH
LSQLEAIKLYLKGKEPLLQCDKELIQEVLFDAVVSAPIEAYWTSLALNKSENSDKGVEVAFLGTRT
GLSRINLFVGAEQLTNQDFLKAGDKENIFNADHFPLWYRRAAEQIPGSFVYSIPFSTGPVNKSNVV
TASTSIQLLDERKSPVVAAVGIQMKLEFFQRKFWTASRQCASLDGKCSISCDDETVNCYLIDNNGF
ILVSEDYTQTGDFFGEIEGAVMNKLLTMGSFKRITLYDYQAMCRANKESSDGAHGLLDPYNAFLSA
VKWIMTELVLFLVEFNLCSWWHSDMTAKAQKLKQTLEPCDTEYPAFVSERTIKETTGNIACEDCSK
SFVIQQIPSSNLFMVVVDSSCLCESVAPITMAPIEIRYNESLKCERLKAQKIRRRPESCHGFHPEE
NARECGGAPSLQAQTVLLLLPLLLMLFSR

(2) INFORMATION FOR SEQ ID NO: 6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH:
(B) TYPE:
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: protein

(ix) FEATURE:

(A) NAME/KEY:

(B) LOCATION:

(D) OTHER INFORMATION: α2δ-D

(iii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:

MPATPNFLANPSSSSRWIPLQPMPVAWAFVQKTSALLWLLLLGTSLSPAWGQAKIPLETVKLWADT
FGGDLYNTVTKYSGSLLLQKKYKDVESSLKIEEVDGLELVRKFSEDMENMLRRKVEAVQNLVEAAE
EADLNHEFNESLVFDYYNSVLINERDEKGNFVELGAEFLLESNAHFSNLPVNTSISSVQLPTNVYN
KDPDILNGVYMSEALNAVFVENFQRDPTLTWQYFGSATGFFRIYPGIKWTPDENGVITFDCRNRGW
YIQAATSPKDIVILVDVSGSMKGLRMTIAKHTITTILDTLGENDFVNIIAYNDYVHYIEPCFKGIL
VQADRDNREHFKLLVEELMVKGVGVVVDQALREAFQILKQFQEAKQGSLCNQAIMLISDGAVEDYEP
VFEKYNWPDCKVRVFTYLIGREVSFADRMKWIACNNKGYYTQISTLADTQENVMEYLHVLSRPMVI
NHDHDIIWTEAYMDSKLLSSQAQSLTLLTTVAMPVFSKKNETRSHGILLGVVGSDVALRELMKLAP
RYKLGVHGYAFLNTNNGYILSHPDLRPLYREGKKLKPKPNYNSVDLSEVEWEDQAESLRTAMINRE
TGTLSMDVKVPMDKGKRVLFLTNDYFFTDISDTPFSLGVVLSRGHGEYILLGNTSVEEGLHDLLHP
DLALAGDWIYCITDIDPDHRKLSQLEAMIRFLTRKDPDLECDEELVREVLFDAVVTAPMEAYWTAL
ALNMSEESEHVVDMAFLGTRAGLLRSSLFVGSEKVSDRKFLTPEDEASVFTLDRFPLWYRQASEHP
AGSFVFNLRWAEGPESAGEPMVVTASTAVAVTVDKRTAIAAAAGVQMKLEFLQRKFWAATRQCSTV
DGPCTQSCEDSDLDCFVIDNNGFILISKRSRETGRFLGEVDGAVLTQLLSMGVFSQVTMYDYQAMC
KPSSHHHSAAQPLVSPISAFLTATRWLLQELVLFLLEWSVWGSWYDRGAEAKSVFHHSHKHKKQDP
LQPCDTEYPVFVYQPAIREANGIVECGPCQKVFVVQQIPNSNLLLLVTDPTCDCSIFPPVLQEATE
VKYNASVKCDRMRSQKLRRRPDSCHAFHPEENAQDCGGASDTSASPPLLLLPVCAWGLLPQLLR

(2) INFORMATION FOR SEQ ID NO: 7

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH:
(B) TYPE:
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

(A) NAME/KEY: Coding Sequence

(B) LOCATION:

(D) OTHER INFORMATION:

(iii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7:

AGGATGGCCCTGGGGAAAAGAAGA

(2) INFORMATION FOR SEQ ID NO: 8

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH:
(B) TYPE:
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

(A) NAME/KEY: Coding Sequence

(B) LOCATION:

(D) OTHER INFORMATION: 3' primer for $\alpha 2\delta$-B

(iii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8:

ATCATCAATGAGGACACAGA

(2) INFORMATION FOR SEQ ID NO: 9

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH:
(B) TYPE:
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:
(A) NAME/KEY: Coding Sequence
(B) LOCATION:
(D) OTHER INFORMATION: 5' primers used for RT-PCR of α2δ-C
(iii) MOLECULE TYPE: cDNA
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9:

AGAACGAAACCAGATCGAAG

(2) INFORMATION FOR SEQ ID NO: 10

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH:
(B) TYPE:
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:
(A) NAME/KEY: Coding Sequence
(B) LOCATION:
(D) OTHER INFORMATION: 3' primer used for RT-PCR of α2δ-C
(iii) MOLECULE TYPE: cDNA
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 10:

CGATTCACCATAGCATTTCTC

(2) INFORMATION FOR SEQ ID NO: 11

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH:
(B) TYPE:
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:
(A) NAME/KEY: Coding Sequence
(B) LOCATION:

(D) OTHER INFORMATION: primer for α2δ-C

(iii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 11:

CTACCAAGCCATGTGTA

(2) INFORMATION FOR SEQ ID NO: 12

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH:
(B) TYPE:
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

(A) NAME/KEY: Coding Sequence

(B) LOCATION:

(D) OTHER INFORMATION: 5' primer to amplify mouse α2δ-C

(iii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 12:

AGAACGAAACTAGGTCAAAG

(2) INFORMATION FOR SEQ ID NO: 13

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH:
(B) TYPE:
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

(A) NAME/KEY: Coding Sequence

(B) LOCATION:

(D) OTHER INFORMATION: 3' primer to amplify mouse α2δ-C

(iii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 13:

CGATTTACCATGGCATTTCGT

(2) INFORMATION FOR SEQ ID NO: 14

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH:
(B) TYPE:
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

(A) NAME/KEY: Coding Sequence

(B) LOCATION:

(D) OTHER INFORMATION: rat sequence for α2δ-C

(iii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 14:

GATTCTTCTGGGTGTGGTTGGCACAGATGTCCCAGTAAAAGAGCTTCTGAAGACCATCCCCAAATA
CAAGTTAGGAATTCATGGTTATGCCTTTGCCATCACGAATAATGGATACATCTTGACACACCCGGA
GCTCAGGCCCCTGTATGAAGAAGGGAAAAAGCGAAGGAAGCCTAATTACAGTAGTGTGGATCTCTC
GGAAGTCGAGTGGGAAGATCGGGATGATGTGTTACGAAATGCCATGGTAAATCGAC

(2) INFORMATION FOR SEQ ID NO: 15

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH:
(B) TYPE:
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

(A) NAME/KEY: Coding Sequence

(B) LOCATION:

(D) OTHER INFORMATION: (1690-1761) α2δ–D, human splice variant

(iii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 15:

CCATGCCTGCAACTCCCAACTTCCTCGCAAACCCCAGCTCCAGCAGCCGCTGGATTCCCCTCCAGC
CAATGCCCGTGGCCTGGGCCTTTGTGCAGAAGACCTCGGCCCTCCTGTGGCTGCTGCTTCTAGGCA
CCTCCCTGTCCCCTGCGTGGGGACAGGCCAAGATTCCTCTGGAAACAGTGAAGCTATGGGCTGACA
CCTTCGGCGGGGACCTGTATAACACTGTGACCAAATACTCAGGCTCTCTCTTGCTGCAGAAGAAGT
ACAAGGATGTGGAGTCCAGTCTGAAGATCGAGGAGGTGGATGGCTTGGAGCTGGTGAGGAAGTTCT
CAGAGGACATGGAGAACATGCTGCGGAGGAAAGTCGAGGCGGTCCAGAATCTGGTGGAAGCTGCCG
AGGAGGCCGACCTGAACCACGAATTCAATGAATCCCTGGTGTTCGACTATTACAACTCGGTCCTGA
TCAACGAGAGGGACGAGAAGGGCAACTTCGTGGAGCTGGGCGCCGAGTTCCTCCTGGAGTCCAATG
CTCACTTCAGCAACCTGCCGGTGAACACCTCCATCAGCAGCGTGCAGCTGCCCACCAACGTGTACA
ACAAAGACCCAGATATTTAAATGGAGTCTACATGTCTGAAGCCTTGAATGCTGTCTTCGTGGAGA
ACTTCCAGAGAGACCCAACGTTGACCTGGCAATATTTTGGCAGTGCAACTGGATTCTTCAGGATCT
ATCCAGGTATAAAATGGACACCTGATGAGAATGGAGTCATTACTTTTGACTGCCGAAACCGCGGCT
GGTACATTCAAGCTGCTACTTCTCCCAAGGACATAGTGATTTTGGTGGACGTGAGCGGCAGTATGA
AGGGGCTGAGGATGACTATTGCCAAGCACACCATCACCACCATCTTGGACACCCTGGGGAGAATG
ACTTCGTTAATATCATAGCGTACAATGACTACGTCCATTACATCGAGCCTTGTTTTAAAGGGATCC
TCGTCCAGGCGGACCGAGACAATCGAGAGCATTTCAAACTGCTGGTGGAGGAGTTGATGGTCAAAG
GTGTGGGGGTCGTGGACCAAGCCCTGAGAGAAGCCTTCCAGATCCTGAAGCAGTTCCAAGAGGCCA
AGCAAGGAAGCCTCTGCAACCAGGCCATCATGCTCATCAGCGACGGCGCCGTGGAGGACTACGAGC
CGGTGTTTGAGAAGTATAACTGGCCAGACTGTAAGGTCCGAGTTTTCACTTACCTCATTGGGAGAG
AAGTGTCTTTTGCTGACCGCATGAAGTGGATTGCATGCAACAACAAAGGCTACTACACGCAGATCT
CAACGCTGGCGGACACCCAGGAGAACGTGATGGAATACCTGCACGTGCTCAGCCGCCCCATGGTCA
TCAACCACGACCACGACATCATCTGGACAGAGGCCTACATGGACAGCAAGCTCCTCAGCTCGCAGG

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH:
(B) TYPE:
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

(A) NAME/KEY: Coding Sequence

(B) LOCATION:

(D) OTHER INFORMATION: human variant α2δ-D, EDGE screen

(iii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 16:

CCATGCCTGCAACTCCCAACTTCCTCGCAAACCCCAGCTCCAGCAGCCGCTGGATTCCCCTCCAGC
CAATGCCCGTGGCCTGGGCCTTTGTGCAGAAGACCTCGGCCCTCCTGTGGCTGCTGCTTCTAGGCA
CCTCCCTGTCCCCTGCGTGGGGACAGGCCAAGATTCCTCTGGAAACAGTGAAGCTATGGGCTGACA
CCTTCGGCGGGGACCTGTATAACACTGTGACCAAATACTCAGGCTCTCTCTTGCTGCAGAAGAAGT
ACAAGGATGTGGAGTCCAGTCTGAAGATCGAGGAGGTGGATGGCTTGGAGCTGGTGAGGAAGTTCT
CAGAGGACATGGAGAACATGCTGCGGAGGAAAGTCGAGGCGGTCCAGAATCTGGTGGAAGCTGCGG
AGGAGGCCGACCTGAACCACGAATTCAATGAATCCCTGGTGTTCGACTATTACAACTCGGTCCTGA
TCAACGAGAGGGACGAGAAGGGCAACTTCGTGGAGCTGGGCGCCGAGTTCCTCCTGGAGTCCAATG
CTCACTTCAGCAACCTGCCGGTGAACACCTCCATCAGCAGCGTGCAGCTGCCCACCAACGTGTACA
ACAAAGACCCAGATATTTTAAATGGAGTCTACATGTCTGAAGCCTTGAATGCTGTCTTCGTGGAGA
ACTTCCAGAGAGACCCAACGTTGACCTGGCAATATTTTGGCAGTGCAACTGGATTCTTCAGGATCT
ATCCAGGTATAAAATGGACACCTGATGAGAATGGAGTCATTACTTTTGACTGCCGAAACCGCGGCT
GGTACATTCAAGCTGCTACTTCTCCCAAGGACATAGTGATTTTGGTGGACGTGAGCGGCAGTATGA
AGGGGCTGAGGATGACTATTGCCAAGCACACCATCACCACCATCTTGGACACCCTGGGGGAGAATG
ACTTCRTTAATATCATAGCGTACAATGACTACGTCCATTACATCGAGCCTTGTTTTAAAGGGATCC
TCGTCCAGGCGGACCGAGACAATCGAGAGCATTTCAAACTGCTGGTGGAGGAGTTGATGGTCAAAG
GTGTGGGGGTCGTGGACCAAGCCCTGAGAGAAGCCTTCCAGATCCTGAAGCAGTTCCAAGAGGCCA
AGCAAGGAAGCCTCTGCAACCAGGCCATCATGCTCATCAGCGACGGCGCCGTGGAGGACTACGAGC
CGGTGTTTGAGAAGTATAACTGGCCAGACTGTAAGGTCCGAGTTTTCACTTACCTCATTGGGAGAG
AAGTGTCTTTTGCTGACCGCATGAAGTGGATTGCATGCAACAACAAAGGCTACTACACGCAGATCT
CAACGCTGGCGGACACCCAGGAGAACGTGATGGAATACCTGCACGTGCTCAGCCGCCCCATGGTCA
TCAACCACGACCACGACATCATCTGGACAGAGGCCTACATGGACAGCAAGCTCCTCAGCTCGCAGG
CTCAGAGCCTGACACTGCTCACCACTGTGGCCATGCCAGTCTTCAGCAAGAAGAACGAAACGCGAT
CCCATGGCATTCTCCTGGGTGTGGTGGGCTCAGATGTGGCCCTGAGAGAGCTGATGAAGCTGGCGC
CCCGGTACAAGCTTGGAGTGCACGGATACGCCTTTCTGAACACCAACAATGGCTACATCCTCTCCC
ATCCCGACCTCCGGCCCCTGTACAGAGAGGGGAAGAAACTAAAACCCAAACCTAACTACAACAGTG
TGGATCTCTCCGAAGTGGAGTGGGAAGACCAGGCTGAATCTCTGAGAACAGCCATGATCAATAGGG
AAACAGGTACTCTCTCGATGGATGTGAAGGTTCCGATGGATAAAGGGAAGCGAGTTCTTTTCCTGA
CCAATGACTACTTCTTCACGGACATCAGCGACACCCCTTTCAGTTTGGGGGTGGTCGTCCCGGG
GCCACGGAGAATACATCCTTCTGGGGAACACGTCTGTGGAAGAAGGCCTGCATGACTTGCTTCACC
CAGACCTGGCCCTGGCCGGTGACTGGATCTACTGCATCACAGATATTGACCCAGACCACCGGAAGC
TCAGCCAGCTAGAGGCCATGATCCCGCTTCCTCACCAGGAAGGACCCAGACCTGGAGTGTGACGAGG
AGCTGGTCCGGGAGGTGCTGTTTGACGCGGTGGTGACAGCCCCCATGGAAGCCTACTGGACAGCGC
TGGCCCTCAACATGTCCGAGGAGTCTGAACACGTGGTGGACATGGCCTTCCTGGGCACCCGGGCTG
GCCTCCTGAGAAGCAGCTTGTTCGTGGGCTCCGAGAAGGTCTCCGACAGGAAGTTCCTGACACCTG
AGGACGAGGCCAGCGTGTTCACCCTGGACCGCTTCCCGCTGTGGTACCGCCAGGCCTCAGAGCATC
CTGCTGGCAGCTTCGTCTTCAACCTCCGCTGGGCAGAAGGACCAGAAAGTGCGGGTGAACCCATGG
TGGTGACGGCAAGCACAGCTGTGGCGGTGACCGTGGACAAGAGGACAGCCATTGCTGCAGCCGCGG
GCGTCCAAATGAAGCTGGAATTCCTCCAGCGCAAATTCTGGGCGGCAACGCGGCAGTGCAGCACTG
TGGATGGGCCGTGCACACAGAGCTGCGAGGACAGTGATCTGGACTGCTTCGTCATCGACAACAACG
GGTTCATTCTGATCTCCAAGAGGTCCCGAGAGACGGGAAGATTTCTGGGGGAGGTGGATGGTGCTG
TCCTGACCCAGCTGCTCAGCATGGGGGTGTTCAGCCAAGTGACTATGTATGACTATCAGGCCATGT
GCAAACCCTCGAGTCACCACCACAGTGCAGCCCAGCCCCTGGTCAGCCCAATTTCTGCCTTCTTGA

CGGCGACCAGGTGGCTGCTGCAGGAGCTGGTGCTTGTGAGTGGGGGTAGACACGGGGCTGGTGGAG
GCTGCATGCGAGGGTGGCTTAGGAGGGTGTCCTTGATCAGGAGGCTGCAAGGTCTCCAGGACAACC
CACTTGCTACCAAGACCCCGGGGAAGGAGGGCACAATCCCTGGGCATGGACGCCACCTCTTCCCTG
CATGCTTGCCCCTGGGAGGGACCTCATTGCTCAACCAGAGCCCTCAAGCAGGGAAGAGGGTGTCCT
GGAGGAGAGGGGATGGGCCGGGGGCTGTCAGGGATACTCCAGCTCCTTGGGAACCCAAGTCGGGAG
GGCTCAGAGGTCTCCGAGATTCAGTCCTGTGTCTGACAGGTTCCTGCTGGAGTGGAGTGTCTGGGG
CTCCTGGTACGACAGAGGGGCCGAGGGTGAGTGCACGGAGCTGCAGGGCCATGTGCTGAAGAGCAG
TGGCATTTTGGTCCACTAACGTGAGACCATTCCCTGTGGGGTGGGTGACAGTGGGGATAGGTGACC
CTGAAGCATCGTTGTTCACATCTCACCCTGCGTGGCCTTCTCTCATCACATCCCTCACTCCTGGCT
CTGTGTGTGACATCATCTTGGGACACCGCCACTCCATGTGCCATCATCACCACCCCATGACATCCT
GCCCTCATGTGCCACCATGTTTTCCTGTGCCGTGTCCACCCTGTGCTGGGCTTATGTTCCGGCCAG
CCAAAAGTGTCTTCCATCACTCCCACAAACACAAGAAGCAGGACCCGCTGCAGCCCTGCGACACGG
AGTACCCCGTGTTCGTGTACCAGCCGG:CCATCCGGGAGGCCAACGGGATCGTGGAGTGCGGGCCC
TGCCAGAAGGTATTTGTGGTGCAGCAGATTCCCAACAGTAACCTCCTCCTCCTGGTGACAGACCCC
ACCTGTGACTGCAGCATCTTCCCACCAGTGCTGCAGGAGGCGACAGAAGTCAAATATAATGCCTCT
GTCAAATGTGACCGGATGCGCTCCCAGAAGCTCCGCCGGCGACCAGACTCCTGCCACGCCTTCCAT
CCAGAGGAGAATGCCCAGGACTGCGGYGGCGCCTCGGACACCTCAGCCTCGCCGCCCCTACTCCTG
CTGCCTGTGTGTGCCTGGGGGCTACTGCCCCAACTCCTGCGGTGACACCACCCAGCCTGACCTGTG
TTTTGGCAAGGTGATCCTTCCAGAGCCATCCCAAAAAGTCAGCACTGACATGGGATGCAGCTAACT
GCAGTTGGGTCGCCCCCAGGCCAACGCTCCTCTCAATCCTGGGCTGGTGGCCCCTGGCTCCGGAGA
ATGCTGGATGGAACAGGAAACCAATCACCTGGCACCACTTTCAAGATGCTTCATGGTGCCCGGTAC
CATCTGCCCTAGGTCTCAACATGAGCATACTTCTGACCTAACCTTCCTGTCTCCTCTTCGGGAAGC
CAGCGTGAGCTCAGCTTGGACCAAGACAAAATAATTTAGTTCTTCCTGTACTCCAGAGTCCAGACC
CAGCCAAGAAAGGGTCAGTTGTTTCTGACCCTTTCTGTCGGAGTGGTCTCTGGTAGAACCCAAGGA
CTTCTGGGTACTGAGAAGCAGCAGCAGAATGAGGCCAAATGCAGAGATGAGGCTAAGGCAAGAATA
TGCCCCAACTAAAGCATAGATTCCCCAAAGTGAGGCTCATGGTGGGAGGCCACTCACCTTCCTAGC
TGCTGCTCGAAAAGGTTTGACTGTGTTGGGGTGGGGGTTGGGTAAGGGAATGGTCAAGACTGAGA
AAGGAATGAAATCCATTCAGGAAATATCGACAGGGCTACACGTGATGTCCCCAAACTGCTGCTATT
GAAGAACTTCCCAAAACTTCTTTACAAAGCCCTAAAGGAAAGTTTGCATCTATGAAAAGCCAATAG
GCTGAGACATCCAATTGCTGCATGGAAATTGATGTACATTCAGGGGACGGCAAAAATAGCTGTAAA
ATAGTGAAAAAGAGCAGTGGTTGTGCTCTTTTCTGGCCAATGATTTACAAAAGAATCTACTTGACT
CTGTCCCTGGAGTGAAATCCTTAGGGTTGGAACTTGTGGGAACATTCCAACTTGCTAAGCAGGGTC
CACTGGGAGGGAAGCTCTATCTGGGAACTCACCCCCAGCGCACACACATCTCCCCCAGGGTCCCAA
GGCCCCGCAGCTTCCTCCCCCGACCAAACCCCAAGACCTGGATCCCAGGAGACAACAGTCTCCACA
TGAGAGCAACATTAAGGGCAAAGCCATGGAGAAATGTGGGAGAGGCCGGCCTCAAATCTTTCCATT
TAACAAACCCCAGTGATGGGTATGGACAGCATGCAGGGCTTTTGGGGCGCTTCCCCCCGCTCCTCC
ATCACCCTCAGCCTCCACACTTCAAAGTTCAAGTTCAAAGCTGTTCAAGTTTCCTACCAGCAAATA
GCCCTAACTTGCCTCTAGAGTAGGCCAAATGCCAACTCTGTAAAACACACTTACATTATCGGTTAC
AGAATGTCACTCTTACCATCATGTCTTGCAACAACCCTGTGAGGGCAGTATTAATGCCCCCTTACA
GCAGAAGACACTGCAGCTCGAAGACAGCTTAAGTGGCAGAATAATGCTAGAACAGCTAAGGTTTAC
ATGTACCAAATAACATGTTTCAGCTCATTCCATCCTCACAACAGCCCCCTGAAAGTGGGTACTATC
ATTAGTCCCATGTTATAGAAACTGCAGCAGAGTTGAAAATTGCCTCCAAATTACCGGAAGAGTGTA
TGAAGATTGAATGTGATGTATTCACGTAACATGCTTGAAACTGCCTGGCATATACTAAACGCTAAA
TAAATACATGCTAACTGCAAAAAAAAAAAAAAAAAAA

(2) INFORMATION FOR SEQ ID NO: 17

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH:
(B) TYPE:
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: protein

(ix) FEATURE:

(A) NAME/KEY:

(B) LOCATION:

(D) OTHER INFORMATION: human variant α2δ-D, EDGE screen

(iii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 17:

MPATPNFLANPSSSSRWIPLQPMPVAWAFVQKTSALLWLLLLGTSLSPAWGQAKIPLETV
KLWADTFGGDLYNTVTKYSGSLLLQKKYKDVESSLKIEEVDGLELVRKFSEDMENMLRR
KVEAVQNLVEAAEEADLNHEFNESLVFDYYNSVLINERDEKGNFVELGAEFLLESNAHFS
NLPVNTSISSVQLPTNVYNKDPDILNGVYMSEALNAVFVENFQRDPTLTWQYFGSATGFF
RIYPGIKWTPDENGVITFDCRNRGWYIQAATSPKDIVILVDVSGSMKGLRMTIAKHTITTIL
DTLGENDFVNIIAYNDYVHYIEPCFKGILVQADRDNREHFKLLVEELMVKGVGVVDQALR
EAFQILKQFQEAKQGSLCNQAIMLISDGAVEDYEPVFEKYNWPDCKVRVFTYLIGREVSF
ADRMKWIACNNKGYYTQISTLADTQENVMEYLHVLSRPMVINHDHDIIWTEAYMDSKLL
SSQAQSLTLLTTVAMPVFSKKNETRSHGILLGVVGSDVALRELMKLAPRYKLGVHGYAFL
NTNNGYILSHPDLRPLYREGKKLKPKPNYNSVDLSEVEWEDQAESKRVLFLTNDYFFTDI
SDTPFSLGVVLSRGHGEYILLGNTSVEEGLHDLLHPDLALAGDWIYCITDIDPDHRKLSQL
EAMIRFLTRKDPDLECDEELVREVLFDAVVTAPMEAYWTALALNMSEESEHVVDMAFLG
TRAGLLRSSLFVGSEKVSDRKFLTPEDEASVFTLDRFPLWYRQASEHPAGSFVFNLRWAE
GPESAGEPMVVTASTAVAVTVDKRTAIAAAAGVQMKLEFLQRKFWAATRQCSTVDGPC
TQSCEDSDLDCFVIDNNGFILISKRSRETGRFLGEVDGAVLTQLLSMGVFSQVTMYDYQA
MCKPSSHHHSAAQPLVSPISAFLTATRWLLQELVLFLLEWSVWGSWYDRGAEAKSVFHH
SHKHKKQDPLQPCDTEYPVFVYQPAIREANGIVECGPCQKVFVVQQIPNSNLLLLVTDPTC
DCSIFPPVLQEATEVKYNASVKCDRMRSQKLRRRPDSCHAFHPEENAQDCGGASDTSASP
PLLLLPVCAWGLLPQLLR

(2) INFORMATION FOR SEQ ID NO: 18

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH:
(B) TYPE:
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

(A) NAME/KEY: Coding Sequence

(B) LOCATION:

(D) OTHER INFORMATION: 5′ primer for human α2δ-D

(iii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 18:

GCGAGGACAGTGATCTGG

(2) INFORMATION FOR SEQ ID NO: 19

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH:
(B) TYPE:
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

(A) NAME/KEY: Coding Sequence

(B) LOCATION:

(D) OTHER INFORMATION: 3' primer for human α2δ-D

(iii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 19:

GGGTCCTCGTTCTTGTGTTT

(2) INFORMATION FOR SEQ ID NO: 20

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH:
(B) TYPE:
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:

(A) NAME/KEY: Coding Sequence

(B) LOCATION:

(D) OTHER INFORMATION: nested primer for human α2δ-D

(iii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 20:

TCAGCCTCCACACTTCAAAG

(2) INFORMATION FOR SEQ ID NO: 21

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH:
(B) TYPE:
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:

(A) NAME/KEY: Coding Sequence

(B) LOCATION:

(D) OTHER INFORMATION: primer for human α2δ-D

(iii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 21:

TCCGCCTGGACGAGGATCC

(2) INFORMATION FOR SEQ ID NO: 22

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH:
(B) TYPE:
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:
(A) NAME/KEY: Coding Sequence
(B) LOCATION:
(D) OTHER INFORMATION: primer for human α2δ-D
(iii) MOLECULE TYPE: cDNA
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 22:

GTGTCCAAGATGGTGGTGAT

(2) INFORMATION FOR SEQ ID NO: 23

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH:
(B) TYPE:
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:
(A) NAME/KEY: Coding Sequence
(B) LOCATION:
(D) OTHER INFORMATION: primer for human α2δ-D (d20)
(iii) MOLECULE TYPE: cDNA
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 23:

ATCTACTGCATCACAGATATTG

(2) INFORMATION FOR SEQ ID NO: 24

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH:
(B) TYPE:
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:
(A) NAME/KEY: Coding Sequence
(B) LOCATION:
(D) OTHER INFORMATION: primer for human α2δ-D (α2δD2)
(iii) MOLECULE TYPE: cDNA
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 24:

GGTGAGGAAGCGGATCATG

(2) INFORMATION FOR SEQ ID NO: 25

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH:
(B) TYPE:
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:
(A) NAME/KEY: Coding Sequence
(B) LOCATION:
(D) OTHER INFORMATION: 5' primer mouse genomic of α2δ-B
(iii) MOLECULE TYPE: cDNA
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 25:

TTCAACGAGAAGGCACAGCCT

(2) INFORMATION FOR SEQ ID NO: 26

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH:
(B) TYPE:
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:
(A) NAME/KEY: Coding Sequence
(B) LOCATION:
(D) OTHER INFORMATION: 3' primer mouse genomic of α2δ-B
(iii) MOLECULE TYPE: cDNA
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 26:

GTTGGCACAGGCCATCCACTG

(2) INFORMATION FOR SEQ ID NO: 27

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH:
(B) TYPE:
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:
(A) NAME/KEY: Coding Sequence
(B) LOCATION:

(D) OTHER INFORMATION: primer for sequencing mouse genomic, based on human

(iii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 27:
AGGCTGTGCCTTCTCGTTGAA

(2) INFORMATION FOR SEQ ID NO: 28

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH:
(B) TYPE:
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:
(A) NAME/KEY: Coding Sequence
(B) LOCATION:
(D) OTHER INFORMATION: primer for sequencing mouse genomic, based on human

(iii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 28:
GAGCCCCCAAGAAGATCG

(2) INFORMATION FOR SEQ ID NO: 29

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH:
(B) TYPE:
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:
(A) NAME/KEY: Coding Sequence
(B) LOCATION:
(D) OTHER INFORMATION: primer for sequencing mouse genomic, based on human

(iii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 29:
CGATCTTCTTGGGGGCTC

(2) INFORMATION FOR SEQ ID NO: 30

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH:
(B) TYPE:
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:
(A) NAME/KEY: Coding Sequence
(B) LOCATION:
(D) OTHER INFORMATION: primer for sequencing mouse genomic, based on human
(iii) MOLECULE TYPE: cDNA
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 30:
CACGATGATGACCATGTC

(2) INFORMATION FOR SEQ ID NO: 31

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH:
(B) TYPE:
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:
(A) NAME/KEY: Coding Sequence
(B) LOCATION:
(D) OTHER INFORMATION: primer for sequencing mouse genomic, based on mouse
(iii) MOLECULE TYPE: cDNA
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 31:
GGCAAGACCCTACACTGTTG

(2) INFORMATION FOR SEQ ID NO: 32

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH:
(B) TYPE:
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:
(A) NAME/KEY: Coding Sequence
(B) LOCATION:

(D) OTHER INFORMATION: primer for sequencing mouse genomic, based on mouse

(iii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 32:

CCTGGTAATAGCGAGTGAC

(2) INFORMATION FOR SEQ ID NO: 33

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH:
(B) TYPE:
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

(A) NAME/KEY: Coding Sequence

(B) LOCATION:

(D) OTHER INFORMATION: 5' genomic sequence from 10kb fragment for mouse α2δ-B

(iii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 33:

AAGCTTCTCTCTCATCACCAGGAGGAAGACATCATGTACTACGATGCCAAGGCTGACG
CCGAGCTGGTAAGTGTCCCCACCTTTGCCGTAGAGGATGGGGAGCAGCCAGAGCCAC
ACCTTGTTCTTCTGGGCCACAACAGTCTCAGCTGTAAAGTGGGTGTTAGGGATCCATG
CTCACCTTTCTGAACTCAACCATTCTGTGTCGTGCTTGGTCAGCCTCTCCTTGTCCACA
GCTCCCTAGAGATCCTTGACCCTCCAGGGCGTGTCTTCATCACCATTATAGGCTAAGC
TCCCCCTGCACCATGTGGAGCAAGCAGGGTGGTAGAGTGTTGGATATCAGGGTGGTTC
CATCCCAGTATGAGGGGCTCTCTGGGCTCCATGGGAGTAGAGAGGAGAAAGAAATGG
ACTCCAGGACCTCCTGGGGTAGGTACATGGGAGTGAGACATGGTGACATCTAAGCCC
TGCCCAGGACAGTAGAGGCTCCTTTCCTTGTGATTTGGGGAACTTTGCATCAAGCTAT
GTAGAAGAACCCATGG

(2) INFORMATION FOR SEQ ID NO: 34

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH:
(B) TYPE:
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

(A) NAME/KEY: Coding Sequence

(B) LOCATION:

(D) OTHER INFORMATION: 3' genomic sequence from 10kb fragment for mouse α2δ-B

(iii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 34:

CAGGTGGCCTGTGGCTGGGCCCCTTCTCTGAACACTCACAGTGGAGACAGGGCTGGCC
ACAGNAGACCCCATCCTTCTCTCCCTTCAGGGGCTGGGGTTGGTGGTAACAGGAACTT
CTCCCTGTTTTCAACCTGACACAGGATGGCCCTGGGGAAAAGAAGGTGAGTTGCCCAG
TGGGTTATCTGGGGAGGAGTTGGCATGCCTGGAGCAGGTCTGGGGATGGAGGAGGGT
TAGGGCATGCTACAGATTTGGCAAAGCAGCTCTCCGTATCAGCAGCTTAGCCCTTAGG
CCTGGGCCAGGGGGTTCTACTATGGAGTTGACTCATTATAGCATACCTTCCCATTCCTT
TGTGTCCAGAACCAGTTAATCCTGGGTGTCATGGGCATCGATGTGGCCTTGAATGACA
TCAAAAGGCTGACTCCCAACTACACAGTAAGTGTCCACCTGCCCCTCTGCCCTGGTTT
GCTGTCCATAGTGACACAAGCCAGACTCAGCAGGGGAGACATGGGGACTGAAAGACC
GTCACAGAAAGACTTCCCAAAGGGTTTGTTCTGAAGCTGTGGACAGCAAGC

(2) INFORMATION FOR SEQ ID NO: 35

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH:
(B) TYPE:
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

(A) NAME/KEY: Coding Sequence

(B) LOCATION:

(D) OTHER INFORMATION: 1.8 kb mouse genomic sequence for mouse α2δ-B

(iii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 35:

GCTTTCTTGTGGCTGCGGGCCTTGGAGTGCATGCTGAGTGGGTGAGCTCCCTGGGGGC
CGGCTGCAGGCTCCAGGCAAGCATGCTGGATGGGGGCCCAGCTCACAGCTCCCTGCC
ACCCAGGCGGCCCTTCTCCACAGGCCACAAACCACATCAGCCCTGCTTGCTCACCGAG
GCCTGGATGAGGGGTAGGCTGAGATATTTCTTTGATGATTTAGAGGAGGGAGAGCAA
GAAAATCTCCCTGGAAGAGCTGGTGTGGCCCCACATGAGATCCTGGGAAATCAAAGA
AAGCCTGGGCAGGCAGAAAGCAGGGGAGGCCATGGAGATGGGTTTAGCAGGGGGCG
ACCCTGAACCTCCCAACCCCAGCCTTCTGCCCTGCCCCTCAGCTACCGTCATCCTCAAT
GAGCTTAACTGGACAGAGGCCCTGGAGAACGTCTTCATTGAGAACCGTAGGCAAGAC
CCTACACTGTTGTGGCAAGTCTTTGGCAGTGCCACGGGAGTCACTCGCTATTACCCAG
GTAGGCACCACTGTCTCCCTGGCCCATCCAGCACCCGTCTTGCTCCATCTCCAAGCCTA
CCCATTCTGAGGTCCATGGGGTACAATGAACCAGGTCAATCCCCATCACTCCCGCCTG
CTCCAGTCAGACCCTTCTGCCGGGCCGGGCCCCTTCACCCCCTCTTTCCACAGCCACAC
CATGGCGAGCCCCCAAGAAGATTGACCTGTACGATGTCAGAAGACGACCCTGGTGAG
TGAGCAAGGGGGGTGGAGGCGAGACACCCCCTCAACTCCCCATCTCTCGTGCCCGCTC
CCCTCCCTCCCAATATCCAGACCTCCGAGCAGGGCGCAGCCAGCTCTATCCAATTTTC
ATTTCACACATCGCTGCCACTGGAAAATGGATCCCATCGCCCAGGCAAGCCGCCCAGC
TGCCTCTGCCCCCACGCGTGTCGTCCACTACCCAGCCCCCCCACACCCACTCAGAACT
GAGAGCAGACCAGGGAAGGTGCTTCCAGGGGTAGCTAGAGCCTCCGTCAGGTCAGCC
GGCCCCACCTACTCATTTGATCCCTGGACACCCCGACCCTCTGCTCTGCCTCTCTCACA
CTACTCCATGATCTTCCCTCCCTCCTCCATTACACAGCCAGACTCTCTGGAGTCTCTCT
AGGACAGAGGACACAAGCCACTAAAGCCTTCTGTCCCCGTGGATCACCTGCCCCTTCC
CCCTCACCTCTTGTTTACTTAATGAGGGAACCAGATCACTCACGTCACAAGAAAAAAA
AAACTGTCTTTTTGTATTGAGCATGGTCTCCCCAGTGCCCAGACCTATTCCAACCCCTG

TAGTGCGTGGTCAGTAGAAACACAGGAATCAAGTGGGTGGAAGAAGGAAGACCCCGC
AGGTCCCGGAGGTGCCGTCCTTAACTGAGTCTTCTCACTGGCAGGTATATACAGGGGG
CCTCATCACCCAAGGACATGGTCATCATTGTGGATGTGTGAGTGAGCCTTGTAGGCTG
GTGGGATGGGCTAGGACTGGACTCTGCTTCCTGGGCACCTTATGAGGGAAGGGCGGG
AAAACCCTGAGAGCCCACATGCATGCGCCCCCTTCCGTGCCTGGTTTCCAGGAGTGGG
AGCGTGAGCGGCCTGACTCTGAAGCTGATGAAGACGTCCGTCTGTGAGATGCTAGAC
ACGCTCTCTGATGATGACTATGTGAACGTGGCCTCAGTGAGTGGCAAGGTGGCAGGC
AGGCTGGGTACCACTCACCCCCATCCAACCTGCTCCCATGACAACCATCAGCCCTGTA
CAACAGCTGCACACTGTGTGGCCAGCCTGAAGCCACTCACCACCCCCCACTGTCCCCA
CAG

(2) INFORMATION FOR SEQ ID NO: 36

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH:
(B) TYPE:
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:
(A) NAME/KEY: Coding Sequence
(B) LOCATION:
(D) OTHER INFORMATION: 5' primers to amplify rat sequences for α2δ-C, PCR 1
(iii) MOLECULE TYPE: cDNA
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 36:
GACAGGACCAACAAGGAGCAC

(2) INFORMATION FOR SEQ ID NO: 37

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH:
(B) TYPE:
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:
(A) NAME/KEY: Coding Sequence
(B) LOCATION:
(D) OTHER INFORMATION: 3' primers to amplify rat sequences for α2δ-C, PCR 1
(iii) MOLECULE TYPE: cDNA
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 37:
GCCAACCACACCCAGAAGAAT

(2) INFORMATION FOR SEQ ID NO: 38

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH:
(B) TYPE:
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

(A) NAME/KEY: Coding Sequence

(B) LOCATION:

(D) OTHER INFORMATION: 5' primers to amplify rat sequences for α2δ-C, PCR 5

(iii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 38:

AACGCACCATCAAGGAGACCA

(2) INFORMATION FOR SEQ ID NO: 39

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH:
(B) TYPE:
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

(A) NAME/KEY: Coding Sequence

(B) LOCATION:

(D) OTHER INFORMATION: 3' primers to amplify rat sequences for α2δ-C, PCR 5

(iii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 39:

AGGGGCAGCAGCAGCAAG

(2) INFORMATION FOR SEQ ID NO: 40

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH:
(B) TYPE:
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

(A) NAME/KEY: Coding Sequence

(B) LOCATION:

(D) OTHER INFORMATION: PCR1 product, rat α2δ-C

(iii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 40:

TTCAGGGAGCATTTGGACAAACTTTTTGCCAAAGGGATTGGAATGCTCGATATTGCGCTGAACGAG
GCCTTCAATGTACTGAGCGATTTCAACCACACCGGACAAGGAAGCATTTGCAGCCAGGCCATTATG
CTCATAACCGATGGGGCARTGGACACCTACGAYACCATCTTTGCAAAGTACAATTGGCCAGAGCGA
AAGGTTCGAATCTTCACTTACCTCATTGGACGAGAGGCTGCTTTTGCAGACAATCTCAAGTGGATR
GCTTGTGCTAACAAAGGATTTTCACCCAGATCTCCACCTTGGCTGATGTGCAGGAAAATGTCATG
GAATACCTCCATGTACTCAGTCGACCCAAAGTCATCGACCAGGAACATGATGTGGTGTGGACCGAA
GCGTACATCGACAGCACTCTCCCTCAGGCTCAAAAGCTTGCTGATGATCAGGGCCTCGTCTTGATG
ACCACAGTGGCCATGCCTGTGTTTAGTAAGCAGAACGAAACTAGGTCAAAGGGC

(2) INFORMATION FOR SEQ ID NO: 41

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH:
(B) TYPE:
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

(A) NAME/KEY: Coding Sequence

(B) LOCATION:

(D) OTHER INFORMATION: PCR5 product, rat α2δ-C

(iii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 41:

CAGGGAACATTGCTTGTGAAGAYTGCTCCAAGTCCTTTGTCATCCAGCAAATCCCAAGTAGCAATC
TGTTCATGGYGGTGGTGGACAGTAGCTGTCTCTGTGAGTCTGTGGCTCCTATCACCATGGCACCCA
TTGAAATCAGGTATAATGAATCCCTTAAGTGTGAACGGTTAAAGGCTCAGAAGATCAGACGACGTC
CGGAATCCTGCCACGGCTTCCATCCTGAGGAGAATGCGAGAGAGTGTGGGGGTGCATCAAGTCTCC
AGGCCCAGGT

(2) INFORMATION FOR SEQ ID NO: 42

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH:
(B) TYPE:
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: protein

(ix) FEATURE:

(A) NAME/KEY:

(B) LOCATION:

(D) OTHER INFORMATION: Human α2δ-D variant

(iii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 42:

MPATPNFLANPSSSSRWIPLQPMPVAWAFVQKTSALLWLLLLGTSLSPAWGQAKIPLETV
KLWADTFGGDLYNTVTKYSGSLLLQKKYKDVESSLKIEEVDGLELVRKFSEDMENMLRR
KVEAVQNLVEAAEEADLNHEFNESLVFDYYNSVLINERDEKGNFVELGAEFLLESNAHFS
NLPVNTSISSVQLPTNVYNKDPDILNGVYMSEALNAVFVENFQRDPTLTWQYFGSATGFF
RIYPGIKWTPDENGVITFDCRNRGWYIQAATSPKDIVILVDVSGSMKGLRMTIAKHTITTI
LDTLGENDFXNIIAYNDYVHYIEPCFKGILVQADRDNREHFKLLVEELMVKGVGVVDQAL
REAFQILKQFQEAKQGSLCNQAIMLISDGAVEDYEPVFEKYNWPDCKVRVFTYLIGREVSF
ADRMKWIACNNKGYYTQISTLADTQENVMEYLHVLSRPMVINHDHDIIWTEAYMDSKLL
SSQAQSLTLLTTVAMPVFSKKNETRSHGILLGVVGSDVALRELMKLAPRYKLGVHGYAFL
NTNNGYILSHPDLRPLYREGKKLKPKPNYNSVDLSEVEWEDQAESLRTAMINRETGTLSM
DVKVPMDKGKRVLFLTNDYFFTDISDTPFSLGVVLSRGHGEYILLGNTSVEEGLHDLLHPD
LALAGDWIYCITDIDPDHRKLSQLEAMIRFLTRKDPDLECDEELVREVLFDAVVTAPMEA
YWTALALNMSEESEHVVDMAFLGTRAGLLRSSLFVGSEKVSDRKFLTPEDEASVFTLDRF
PLWYRQASEHPAGSFVFNLRWAEGPESAGEPMVVTASTAVAVTVDKRTAIAAAAGVQM
KLEFLQRKFWAATRQCSTVDGPCTQSCEDSDLDCFVIDNNGFILISKRSRETGRFLGEVDG
AVLTQLLSMGVFSQVTMYDYQAMCKPSSHHHSAAQPLVSPISAFLTATRWLLQELVLVS
GGRHGAGGGCMRGWLRRVSLIRRLQGLQDNPLATKTPGKEGTIPGHGRHLFPACLPLGG
TSLLNQSPQAGKRVSWRRGDGPGAVRDTPAPWEPKSGGLRGLRDSVLCLTGSCWSGVSG
APGTTEGPRVSARSCRAMC

(2) INFORMATION FOR SEQ ID NO: 43:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH:
(B) TYPE:
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

(A) NAME/KEY: Coding Sequence

(B) LOCATION:

(D) OTHER INFORMATION:>1907 α2δ-C, potent. soluble form

(iii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 43:

TACTATAGGGCGGCCGCGAATTCGGCACGAGGCGGCGCGGAGCGGAGCAGGCAGCCCCGCGCGCTC
GCCCACCGCCCGCTCCGCGCAGCTCCCCGCGGCCGCTCTCGTCGCCGCCGCAGCGGGCGCGTCGGA
GGGAGCCCAGCATGGCCGGGCCGGGCTCGCCGCGCCGCGCGTCCCGGGGGGCCTCGGCGCTTCTCG
CTGCCGCGCTTCTCTACGCCGCGCTGGGGGACGTGGTGCGCTCGGAGCAGCAGATACCGCTCTCCG
TGGTGAAGCTCTGGGCCTCGGCTTTTGGTGGGGAGATAAAATCCATTGCTGCTAAGTACTCCGGTT
CCCAGCTTCTGCAAAAGAAATACAAAGAGTATGAGAAAGACGTTGCCATAGAAGAAATTCATGGCC
TCCAACTGGTAAAGAAGCTGGCAAAGAACATGGAAGAGATGTTTCACAAGAAGTCTGAGGCCGTCA
GGCGTCTGGTGGAGGCTGCAGAAGAAGCACACCTGAAACATGAATTTGATGCAGACTTACAGTATG
AATACTTCAATGCTGTGCTGATAAATGAAAGGGACAAAGACGGGAATTTTTTGGAGCTGGGAAAGG
AATTCATCTTAGCCCCAAATGACCATTTTAATAATTTGCCTGTGAACATCAGTCTAAGTGACGTCC
AAGTACCAACGAACATGTACAACAAAGACCCTGCAATTGTCAATGGGGTTTATTGGTCTGAATCTC
TAAACAAAGTTTTTGTAGATAACTTTGACCGTGACCCATCTCTCATATGGCAGTACTTTGGAAGTG
CAAAGGGCTTTTTTAGGCAGTATCCGGGGATTAAATGGGAACCAGATGAGAATGGAGTCATTGCCT
TCGACTGCAGGAACCGAAAATGGTACATCCAGGCAGCAACTTCTCCGAAAGACGTGGTCATTTTAG
TTGACGTCAGTGGCAGCATGAAAGGACTCCGTCTGACTATCGCGAAGCAAACAGTCTCATCCATTT
TGGATACACTTGGGGATGATGACTTCTTCAACATAATTGCTTATAATGAGGAGCTTCACTATGTGG
AACCTTGCCTGAATGGAACTTTGGTGCAAGCCGACAGGACAAACAAAGAGCACTTCAGGGAGCATC

TGGACAAACTTTTCGCCAAAGGAATTGGAATGTTGGATATAGYTCTGAATGAGGCCTTCAACATTC
TGAGTGATTTCAACCACACGGGACAAGGAAGTATCTGCAGTCAGGCCATCATGCTCATAACTGATG
GGGCGGTGGACACCTATGATACAATCTTTGCAAAATACAATTGGCCAGATCGAAAGGTTCGCATCT
TCACATACCTCATTGGACGAGAGGCTGCGTTTGCAGACAATCTAAAGTGGATGGCCTGTGCCAACA
AAGGATTTTTTACCCAGATCTCCACCTTGGCTGATGTGCAGGAGAATGTCATGGAATACCTTCACG
TGCTTAGCCGGCCCAAAGTCATCGACCAGGAGCATGATGTGGTGTGGACCGAAGCTTACATTGACA
GCACTCTGACTGATGATCAGGGCCCCGTCCTGATGACCACTGTAGCCATGCCTGTGTTTAGTAAGC
AGAACGAAACCAGATCGAAGGGCATTCTTCTGGGAGTGGTTGGCACAGATGTCCCAGTGAAAGAAC
TTCTGAAGACCATCCCCAAATACAAGTTAGGGATTCACGGTTATGCCTTTGCAATCACAAATAATG
GATATATCCTGACGCATCCGGAACTCAGGCTGCTGTACGAAGAAGGAAAAAAGCGAAGGAAACCTA
ACTATAGTAGCGTTGACCTCTCTGAGGTGGAGTGGGAAGACCGAGATGACGTGTTGAGAAATGCTA
TGGTGAATCGAAAGACGGGGAAGTTTTCCATGGAGGTGAAGAAGACAGTGGACAAAGGGGTACATT
TTTCTCAAACATTTTTGCTGCTTAATTTAAAACAAACCACTGTGAAAAATTAGCTTTGAAAGCTAT
ATCTGGAATAAATATCTTTCGCTGAAGG

(2) INFORMATION FOR SEQ ID NO: 44:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH:
(B) TYPE:
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:
(A) NAME/KEY: Coding Sequence
(B) LOCATION:
(D) OTHER INFORMATION:α2δ-C,(2686-2745,2892-3001)
(iii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 44:

TACTATAGGGCGGCCGCGAATTCGGCACGAGGCGGCGCGGAGCGGAGCAGGCAGCCCCGCGCGCTC
GCCCACCGCCCGCTCCGCGCAGCTCCCCGCGGCCGCTCTCGTCGCCGCCGCAGCGGGCGCGTCGGA
GGGAGCCCAGCATGGCCGGGCCGGGCTCGCCCGCCGCCGCGCGTCCCGGGGGGGCCTCGGCGCTTCTCG
CTGCCGCGCTTCTCTACGCCGCGCTGGGGGACGTGGTGCGCTCGGAGCAGCAGATACCGCTCTCCG
TGGTGAAGCTCTGGGCCTCGGCTTTTGGTGGGGAGATAAAATCCATTGCTGCTAAGTACTCCGGTT
CCCAGCTTCTGCAAAAGAAATACAAAGAGTATGAGAAAGACGTTGCCATAGAAGAAATTGATGGCC
TCCAACTGGTAAAGAAGCTGGCAAAGAACATGGAAGAGATGTTTCACAAGAAGTCTGAGGCCGTCA
GGCGTCTGGTGGAGGCTGCAGAAGAAGCACACCTGAAAACATGAATTTGATGCAGACTTACAGTATG
AATACTTCAATGCTGTGCTGATAAATGAAAGGGACAAAGACGGGAATTTTTTGGAGCTGGGAAAGG
AATTCATCTTAGCCCCAAATGACCATTTTAATAATTTGCCTGTGAACATCAGTCTAAGTGACGTCC
AAGTACCAACGAACATGTACAACAAAGACCCTGCAATTGTCAATGGGGTTTATTGGTCTGAATCTC
TAAACAAAGTTTTTGTAGATAACTTTGACCGTGACCCATCTCTCATATGGCAGTACTTTGGAAGTG
CAAAGGGCTTTTTTTAGGCAGTATCCGGGGATTAAATGGGAACCAGATGAGAATGGAGTCATTGCCT
TCGACTGCAGGAACCGAAAATGGTACATCCAGGCAGCAACTTCTCCGAAAGACGTGGTCATTTTAG
TTGACGTCAGTGGCAGCATGAAAGGACTCCGTCTGACTATCGCGAAGCAAACAGTCTCATCCATTT
TGGATACACTTGGGGATGATGACTTCTTCAACATAATTGCTTATAATGAGGAGCTTCACTATGTGG
AACCTTGCCTGAATGGAACTTTGGTGCAAGCCGACAGGACAAACAAAGAGCACTTCAGGGAGCATC
TGGACAAACTTTTCGCCAAAGGAATTGGAATGTTGGATATAGCTCTGAATGAGGCCTTCAACATTC
TGAGTGATTTCAACCACACGGGACAAGGAAGTATCTGCAGTCAGGCCATCATGCTCATAACTGATG
GGGCGGTGGACACCTATGATACAATCTTTGCAAAATACAATTGGCCAGATCGAAAGGTTCGCATCT
TCACATACCTCATTGGACGAGAGGCTGCGTTTGCAGACAATCTAAAGTGGATGGCCTGTGCCAACA
AAGGATTTTTTACCCAGATCTCCACCTTGGCTGATGTGCAGGAGAATGTCATGGAATACCTTCACG
TGCTTAGCCGGCCCAAAGTCATCGACCAGGAGCATGATGTGGTGTGGACCGAAGCTTACATTGACA

GCACTCTGACTGATGATCAGGGCCCCGTCCTGATGACCACTGTAGCCATGCCTGTGTTTAGTAAGC
AGAACGAAACCAGATCGAAGGGCATTCTTCTGGGAGTGGTTGGCACAGATGTCCCAGTGAAAGAAC
TTCTGAAGACCATCCCCAAATACAAGTTAGGGATTCACGGTTATGCCTTTGCAATCACAAATAATG
GRTATATCCTGACGCATCCGGAACTCAGGCTGCTGTACGAAGAAGGAAAAAAGCGAAGGAAACCTA
ACTATAGTAGCGTTGACCTCTCTGAGGTGGAGTGGGAAGACCGAGATGACGTGTTGAGAAATGCTA
TGGTGAATCGAAAGACGGGGAAGTTTTCCATGGAGGTGAAGAAGACAGTGGACAAAGGGAAACGGG
TTTTGGTGATGACAAATGACTACTATTATACAGACATCAAGGGTACTCCTTTCAGTTTAGGTGTGG
CGCTTTCCAGAGGTCATGGGAAATATTTCTTCCGAGGGAATGTAACCATCGAAGAAGGCCTGCATG
ACTTAGAACATCCCGATGTGTCCTTGGCAGATGAATGGTCCTACTGCAACACTGACCTACACCCTG
AGCACCGCCATCTGTCTCAGTTAGAAGCGATTAAGCTCTACCTAAAAGGCAAAGAACCTCTGCTCC
AGTGTGATAAAGAATTGATCCAAGAAGTCCTTTTTGACGCGGTGGTGAGTGCCCCCATTGAAGCGT
ATTGGACCAGCCTGGCCCTCAACAAATCTGAAAATTCTGACAAGGGCGTGGAGGTTGCCTTCCTCG
GCACTCGCACGGGCCTCTCCAGAATCAACCTGTTTGTCGGGGCTGAGCAGCTCACCAATCAGGACT
TCCTGAAAGCTGGCGACAAGGAGAACATTTTTAACGCAGACCATTTCCCTCTCTGGTACCGAAGAG
CCGCTGAGCAGATTCCAGGGAGCTTCGTCTACTCGATCCCATTCAGCACTGGACCAGTCAATAAAA
GCAATGTGGTGACAGCAAGTACATCCATCCAGCTCCTGGATGAACGGAAATCTCCTGTGAGTGCAG
CTGTAGGCATTCAGATGAAACTTGAATTTTTCCAAAGGAAGTTCTGGACTGCCAGCAGACAGTGTG
CTTCCCTGGATGGCAAATGCTCCATCAGCTGTGATGATGAGACTGGAGACTTTTTGGTGAGATCG
AGGGAGCTGTGATGAACAAATTGCTAACAATGGGCTCCTTTAAAAGAATTACCCTTTATGACTACC
AAGCCATGTGTAGAGCCAACAAGGAAAGCAGCGATGGCGCCCATGGCCTCCTGGATCCCAGAAATT
GAAACAGACCCTGGAGCCTTGTGATACTGAATATCCAGCATTCGTCTCTGAGCGCACCATCAAGGA
GACTACAGGGAATATTGCTTGTGAAGACTGCTCCAAGTCCTTTGTCATCCAGCAAATCCCAAGCAG
CAACCTGTTCATGGTGGTGGTGGACAGCAACTGCCTCTGTGAATCTGTGGCCCCCATCACCATGGC
ACCCATTGAAATCAGGTATAATGAATCCCTTAAGTGTGAACGTCTAAAGGCCCAGAAGATCAGAAG
GCGCCCAGAATCTTGTCATGGCTTCCATCCTGAGGAGAATGCAAGGGAGTGTGGGGGTGCGCCGAG
TCTCCAAGCCCAGACAGTCCTCCTTCTGCTCCCTCTGCTTTTGATGCTCTTCTCAAGGTGACACTG
ACTGAGATGTTCTCTTACTGACTGAGATGTTCTCTTGGCATGCTAAATCATGGATAAACTGTGAAC
CAAAATATGGTGCAACATACGAGACATGAATATAGTCCAACCATCAGCATCTCATCATGATTTTAA
ACTGTGCGTGATATAAACTCTTAAAGATATGTTGACAAAAAGTTATCTATCATCTTTTTACTTTGC
CAGTCATGCAAATGTGAGTTTGCCACATGATAATCACCCTTCATCAGAAATGGGACCGCAAGTGGT
AGGCAGTGTCCCTTCTGCTTGAAACCTATTGAAACCAATTTAAAACTGTGTACTTTTTAAATAAAG
TATATTAAAATCATAAAAAAAAAAAAAAAAAAAA

(2) INFORMATION FOR SEQ ID NO: 45:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH:
(B) TYPE:
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:
(A) NAME/KEY: Coding Sequence
(B) LOCATION:
(D) OTHER INFORMATION:adapter primer
(iii) MOLECULE TYPE: cDNA
(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 45:

CCATCCTAATACGACTCACTATAGGGC

(2) INFORMATION FOR SEQ ID NO: 46:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH:
(B) TYPE:
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:
(A) NAME/KEY: Coding Sequence
(B) LOCATION:
(D) OTHER INFORMATION:adapter primer
(iii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 46:
ACTCACTATAGGGCTCGAGCGGC

(2) INFORMATION FOR SEQ ID NO: 47:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH:
(B) TYPE:
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:
(A) NAME/KEY: Coding Sequence
(B) LOCATION:
(D) OTHER INFORMATION: probe for Northern blot
(iii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 47:
CTGTGAGTGCAGCTGTAGGCATTCAGATGAAACTTGAATTTTTCCAAAGGAAGTTCTGGACTGCCA
GCAGACAGTGTGCTTCCCTGGATGGCAAATGCTCCATCAGCTGTGATGATGAGACTGGAGACTTTT
TTGGTGAGATCGAGGGAGCTGTGATGAACAAATTGCTAACAATGGGCTCCTTTAAAAGAATTACCC
TTTATGACTACCAAGCCATGTGTAGAGCCAACAAGGAAAGCAGCGATGGCGCCCATGGCCTCCTGG
ATCCCAGAAATTGAAACAGACCCTGGAGCCTTGTGATACTGAATATCCAGCATTCGTCTCTGAGCG
CACCATCAAGGAGACTACAGGGAATATTGCTTGTGAAGACTGCTCCAAGTCCTTTGTCATCCAGCA
AATCCCAAGCAGCAACCTGTTCATGGTGGTGGTGGACAGCAACTGCCTCTGTGAATCTGTGGCCCC
CATCACCATGGCACCCATTGAAATCAGGTATAATGAATCCCTTAAGTGTGAACGTCTAAAGGCCCA
GAAGATCAGAAGGCGCCCAGAATCTTGTCATGGCTTCCATCCTGAGGAGAATGCAAGGGAGTGTGG
GGGTGCGCCGAGTCTCCAAGCCCAGACAGTCCTCCTTCTGCTCCCTCTGCTTTTGATGCTCTTCTC
AAGGTGACACTGACTGAGATGTTCTCTTACTGACTGAGATGTTCTCTTGGCATGCTAAATCATGGA
TAAACTGTGAACCAAAATATGGTGCAACATACGAGACATGAATATAGTCCAACCATCAGCATCTCA
TCATGATTTTAAACTGTGCGTGATATAAACTCTTAAAGATATGTTGACAAAAAGTTATCTATCATC
TTTTTACTTTGCCAGTCATGCAAATGTGAGTTTGCCACATGATAATCACCCTTCATCAGAAATGGG
ACCGCAAGTGGTAGGCAGTGTCCCTTCTGCTTGAAACCTATTGAAACCAATTTAAAACTGTGTACT
TTTTAAATAAAGTATATTAAAATCATAAAAAAAAAAAAAAAAAAA

(2) INFORMATION FOR SEQ ID NO: 48:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH:
(B) TYPE:
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:
(A) NAME/KEY: Coding Sequence
(B) LOCATION:
(D) OTHER INFORMATION: Edge 5' primer
(iii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 48:
CTAGAGGCCATGATCCGCTTCCTCAC

(2) INFORMATION FOR SEQ ID NO: 49:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH:
(B) TYPE:
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: cDNA
(ix) FEATURE:
(A) NAME/KEY: Coding Sequence
(B) LOCATION:
(D) OTHER INFORMATION: Edge 3' primer
(iii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 49:
GCCCACGAACAAGCTGCTTC